EAST Search History

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	15	(johnson schoepp).in. and antipsychotic.ti.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2007/06/06 13:04

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'BI BIEX' IS DEFAULT SEARCH FIELD FOR 'WPIX' FILE

=> d max l14

L14  ANSWER 1 OF 1  WPIX COPYRIGHT 2007      THE THOMSON CORP on STN
AN   2003-812683 [76]   WPIX
ED   20050706
DNC  C2003-225997 [76]
TI   Pharmaceutical composition useful for treating psychiatric disorders
     comprises atypical antipsychotic and mGlu2/3 receptor agonist
DC   B05
IN   JOHNSON B G; SCHOEPP D D
PA   (JOHN-I) JOHNSON B G; (ELIL-C) LILLY & CO ELI
     ; (SCHO-I) SCHOEPP D D
CYC  102
PI   WO--2003084610  A1 20031016 (200376)* EN  21[8]
     AU--2003218063  A1 20031020 (200436)  EN
     EP-----1492595  A1 20050105 (200504)  EN
     US-20050192273  A1 20050901 (200558)  EN
     JP--2005528378  W  20050922 (200563)  JA  25
ADT  WO--2003084610 A1 2003WO-US0007283  20030321; US-20050192273 A1
     Provisional 2002US-000369771P 20020403; AU--2003218063 A1 2003AU-000218063
     20030321; EP-----1492595 A1 2003EP-000714045  20030321; JP--2005528378 W
     2003JP-000581846  20030321; EP-----1492595 A1 2003WO-US0007283  20030321;
     US-20050192273 A1 2003WO-US0007283  20030321; JP--2005528378 W
     2003WO-US0007283  20030321; US-20050192273 A1 2004US-000509772  20040928
FDT  AU--2003218063 A1 Based on WO--2003084610 A; EP-----1492595 A1 Based on
     WO--2003084610 A; JP--2005528378 W Based on WO--2003084610 A
PRAI 2002US-000369797P 20020403
     2002US-000369771P 20020403
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2004US-000509772 20040928

IC ICM **A61K-045/06**

IPCR A61K-0031/185 [I,C]; A61K-0031/195 [I,A]; A61K-0031/196 [I,A]; A61K-0031/343 [I,A]; A61K-0031/343 [I,C]; A61K-0031/5415 [I,A]; A61K-0031/5415 [I,C]; A61K-0031/551 [I,A]; A61K-0031/551 [I,C]; A61K-0031/5513 [I,A]; A61K-0038/00 [I,A]; A61K-0038/00 [I,C]; **A61K-0045/00** [I,C]; **A61K-0045/06** [I,A]; A61P-0025/00 [I,C]; **A61P-0025/18** [I,A]; C07D-0243/00 [I,C]; C07D-0243/38 [I,A]; C07D-0307/00 [I,C]; C07D-0307/93 [I,A]; C07D-0495/00 [I,C]; C07D-0495/04 [I,A]

AB WO 2003084610 A1 UPAB: 20060120

NOVELTY - A pharmaceutical composition comprises an atypical antipsychotic (A) and a **mGlu2**/3 receptor agonist (B).

ACTIVITY - Antipsychotic; Neuroleptic; Antimanic; Antidepressant; Gynecological; Anabolic; Eating-Disorders-Gen.; Tranquilizer. Rat model suffering from schizophrenia was administered with phencyclidine (PCP) (5 mg/kg) subcutaneously. Clozapine (I) (3 mg/kg), LY404039 (RTM; (1R,4S,5S,6S)-4-((2'S)-(2'-amino)-propionyl)amino-(2-sulfonylbicyclo(3.1.0)hexane)-4,6-dicarboxylic acid) (II) (1 mg/kg) and combination of (I) and (II) were administered to the rat model. Synergy of (I) and (II) was determined in terms of effects on PCP induction of motor ambulation. (I) had a small impact on PCP-induced ambulations; (II) had statistically insignificant effect on PCP-induced ambulation; and the combination of (I) and (II) reduced PCP-induced ambulation to a level even less than (I) (10 mg/kg) alone.

MECHANISM OF ACTION - **mGlu2**/3 Agonist.

USE - For treating psychiatric disorders (claimed); bipolar disorders; mania; schizophrenia, anxiety, psychosis, obsessive compulsive disorder, schizoaffective disorders associated by the occurrence of a depressive episode during the period of illness; depression with psychotic features; premenstrual syndrome (PMS); anorexia nervosa; and aggression/violence associated with mania, schizophrenia, schizoaffective disorders, substance abuse, head injury, and mental retardation.

ADVANTAGE - The composition has decreased drug related side effects at efficacious doses, thus conferring a marked and unexpected benefit on the patient. The composition provides a potentiation of the increase in the efficacy of (A), by administration of (B).

ABEX ADMINISTRATION - Administration of the composition is 25-300 mg orally, transdermally, percutaneously, intravenously, intramuscularly, intranasally, intrarectally, rectally, subcutaneously, buccally, or by continuous infusion.

SPECIFIC COMPOUNDS - Use of clozapine and **olanzapine** is specifically claimed as (A). Use of (1R,4S,5S,6S)-4-((2'S)-(2'-amino)-propionyl)amino-(2-sulfonylbicyclo(3.1.0)hexane)-4,6-dicarboxylic acid, (1R,4R,5S,6R)-4-amino-(2-oxabicyclo(3.1.0)hexane)-4,6-dicarboxylic acid, (1S,2R,4S,5S,6S)-2-amino-(4-fluorobicyclo(3.1.0)hexane)-2,6-dicarboxylic acid, (+)-2-aminobicyclo(3.1.0)hexane-2,6-dicarboxylic acid, and (1S,2R,4S,6S)-2-amino-4-fluorobicyclo(3.1.0)hexane-2,6-dicarboxylic acid is specifically claimed as (B).

EXAMPLE - No relevant example given.

IT UPIT 20060120

83270-CL; 111168-CL; 266029-CL; 126839-CL; 608576-CL; 196854-CL

FS CPI

MC CPI: B06-H; B10-B02E; B14-E11; B14-J01; B14-J01A1; B14-J01B3; B14-J01B4; B14-L01; B14-M01C

CMC UPB 20060120

M2 *01* D011 D022 E240 F011 F014 F553 H1 H121 H181 H2 H202 H6 H602 H641 L943 M210 M211 M273 M281 M320 M412 M431 M511 M521 M530 M540 **M782** P440 P446 P448 P450 P451 P646 P711 M905 M904
RIN: 03676
DCN: R22668-K R22668-M R22668-T
DCR: 83270-K 83270-M 83270-T

M2 *02* D011 D012 E850 F011 F014 F553 H1 H121 H181 H2 H202 L943 M210 M211 M240 M273 M281 M320 M412 M431 M511 M521 M530 M540 **M782** P440 P446 P448 P450 P451 P646 P711 M905 M904
RIN: 46639

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                DCN: RA04JZ-K RA04JZ-M RA04JZ-T
                DCR: 111168-K 111168-M 111168-T
     M2 *03*    C811 G031 G033 G034 G036 G038 G039 G060 G600 H1 H100 H161 J0
                J012 J1 J152 M280 M320 M415 M431 M510 M520 M530 M541
                M782 P440 P446 P448 P450 P451 P646 P711  M905 M904
                RIN: 00695
                DCN: RA1DQ9-K RA1DQ9-M RA1DQ9-T
                DCR: 266029-K 266029-M 266029-T
     M2 *04*    G031 G038 G039 G060 G600 H1 H100 H161 J0 J012 J1 J152 M280 M320
                M415 M431 M510 M520 M530 M541 M782 P440 P446 P448 P450
                P451 P646 P711  M905 M904
                RIN: 00695
                DCN: RA0W81-K RA0W81-M RA0W81-T
                DCR: 126839-K 126839-M 126839-T
     M2 *05*    C316 D013 D016 D019 D021 D030 D330 H1 H100 H121 J0 J012 J1 J111
                J151 K0 K4 K441 M280 M320 M412 M431 M511 M520 M530 M540
                M782 P440 P446 P448 P450 P451 P646 P711  M905 M904
                RIN: 00693
                DCN: RAC5H7-K RAC5H7-M RAC5H7-T
                DCR: 608576-K 608576-M 608576-T
     M2 *06*    D011 D016 D021 D030 D130 H1 H100 H121 J0 J012 J1 J111 J151 M280
                M320 M412 M431 M511 M520 M530 M540 M782 P440 P446 P448
                P450 P451 P646 P711  M905 M904
                RIN: 07855
                DCN: RA2PDI-K RA2PDI-M RA2PDI-T
                DCR: 196854-K 196854-M 196854-T


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L20  ANSWER 1 OF 21  WPIX COPYRIGHT 2007       THE THOMSON CORP on STN
AN   2004-316075 [29]   WPIX
DNC  C2004-119892 [29]
TI   New pyrimidinylpiperazine derivatives are metabotropic
     glutamate 5 receptor inhibitors useful for the treatment of e.g.
     pain, schizophrenia, anxiety and an addictive disorder
DC   B02; B03
IN   CHEN Z; TAFESSE L
PA   (CHEN-I) CHEN Z; (EURO-N) EUROCELTIQUE SA; (TAFE-I) TAFESSE L
CYC  104
PI   WO--2004029044  A1 20040408 (200429)* EN  272[0]
     US-20040127501  A1 20040701 (200444)  EN
     AU--2003299100  A1 20040419 (200462)  EN
     EP-----1542991  A1 20050622 (200541)  EN
     JP--2006506354  W  20060223 (200619)  JA  251
ADT  WO--2004029044 A1 2003WO-US0030187  20030924; US-20040127501 A1
     Provisional 2002US-000413193P 20020924; US-20040127501 A1
     Provisional 2003US-000456042P 20030319; US-20040127501 A1 2003US-000669875
     20030923; AU--2003299100 A1 2003AU-000299100  20030924; EP-----1542991 A1
     2003EP-000798728  20030924; EP-----1542991 A1 2003WO-US0030187  20030924;
     JP--2006506354 W 2003WO-US0030187  20030924; JP--2006506354 W
     2004JP-000539883  20030924
FDT  AU--2003299100 A1 Based on WO--2004029044 A; EP-----1542991 A1 Based on
     WO--2004029044 A; JP--2006506354 W Based on WO--2004029044 A
PRAI 2003US-000456042P 20030319
       2002US-000413193P 20020924
     2003US-000669875  20030923
IPCI A61K-0031/506 [I,A]; A61K-0031/513 [I,A]; A61P-0001/00 [I,C]; A61P-0001/08
     [I,A]; A61P-0021/00 [I,C]; A61P-0021/02 [I,A]; A61P-0021/04 [I,A];
     A61P-0025/00 [I,A]; A61P-0025/02 [I,A]; A61P-0025/04 [I,A]; A61P-0025/06
     [I,A]; A61P-0025/08 [I,A]; A61P-0025/14 [I,A]; A61P-0025/16 [I,A];
     A61P-0025/18 [I,A]; A61P-0025/22 [I,A]; A61P-0025/24 [I,A];
     A61P-0025/28 [I,A]; A61P-0025/30 [I,A]; A61P-0027/00 [I,C]; A61P-0027/02
     [I,A]; A61P-0029/00 [I,A]; A61P-0043/00 [I,A]; C07D-0239/00 [I,C];
     C07D-0239/00 [I,C]; C07D-0239/42 [I,A]; C07D-0239/47 [I,A]; C07D-0403/00
     [I,C]; C07D-0403/04 [I,A]
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IPCR A61P-0025/00 [I,C]; A61P-0025/22 [I,A]; C07D-0239/00 [I,C]; C07D-0239/42 [I,A]; C07D-0239/46 [I,A]; C07D-0401/00 [I,C]; C07D-0401/12 [I,A]; C07D-0401/14 [I,A]; C07D-0403/00 [I,C]; C07D-0403/04 [I,A]

AB WO 2004029044 A1 UPAB: 20060121

NOVELTY - Pyrimidinylpiperazine derivatives (I) and their salts are new.

DETAILED DESCRIPTION - Pyrimidinylpiperazine derivatives of formula (I) and their salts are new.

A = -C(O)-, -C(S)-, -CH2-, -CH(1-4C alkyl) or C(1-4C alkyl)(1-4C alkyl)-;

n = 0-3;

R1 = (1-3C)alkyl, -O-(1-3C)alkyl, halo, -C(halo)3, -CH(halo)2, -CH2(halo), -NO2, -OH or -CN;

R3 = OH, halo, NO2, CN, NH2, (1-3C alkyl) or CH2OH;

R4 = (1-6C)alkyl, (2-6C)alkenyl, (2-6C)alkynyl, (3-8C)cycloalkyl, -(5-8C)cycloalkenyl, phenyl, (3-5C)heterocycle, C(halo)3, -CH(halo)3, CH2(halo), CN, OH, halo, N3, NO2, N(R6)2, -CH=NR6, NR6OH, COR6, C(O)OR6, -OC(O)R6, -OC(O)OR6, SR6, -S(O)R6 or -S(O)2R6;

R5 = CN, OH, halo, N3, NO2, N(R6)2, CH=NR6, -NR6OH, COR6, C(O)OR6, -OC(O)R6, -OC(O)OR6, -SR6, -S(O)R6 or -S(O)2R6;

R6 = H, (1-6C)alkyl, -(2-6C)alkenyl, -(2-6C)alkynyl, (3-8C)cycloalkyl, (5-8C)cycloalkenyl, phenyl, (3-5C)heterocycle, C(halo)3, CH(halo)2 or CH2(halo);

halo = F, Cl, Br or I; and

p = 0-2.

Provided that when A = -CH2-, -CH(1-4C alkyl) or -C(1-4C alkyl)(1-4C alkyl)-; R2 = phenyl, naphthyl or (14C)aryl (optionally substituted with R4 groups); when A = C(O) or C(S), then R2 = H, -(1-10C)alkyl, -(2-10C)alkenyl, -(3-10C)alkynyl, (8-14C)cycloalkyl, (8-14C)bicycloalkyl, (8-14C)tricycloalkyl, (5-10C)cycloalkenyl, -(8-14C)bicycloalkenyl, (8-14C)tricycloalkenyl, (3-7-membered)heterocycle or -(7-10- membered)bicycloheterocycle, each of which, other than -H, is optionally substituted with R5 groups, or phenyl, naphthyl, (14C)aryl or -(5-10-membered)heteroaryl (optionally substituted with R4 groups).

INDEPENDENT CLAIMS are also included for:

(1) the kit comprising a container containing the composition of (I);

(2) method of preparing composition of (I);

(3) the composition comprising (I); and

(4) method for inhibiting **metabotropic glutamate** 5 (**mGluR5**)-receptor function in a cell, comprising contacting a cell capable of expressing **mGluR5** with (I).

ACTIVITY - Analgesic; Antiparkinsonian; Antiaddictive; Neuroleptic; Tranquilizer.

MECHANISM OF ACTION - **Metabotropic glutamate** 5 (**mGluR5**)-receptor inhibitor; **Metabotropic glutamate** 5 (**mGluR5**)-receptor inhibitor.

(I) were assessed for the mGuR5-receptor antagonist in Sprague-Dawley 18 days old embryos. The median inhibitory concentration of 2-(4-(3-phenylprop-2-ynoyl)piperazin-1-yl)pyrimidine was 554.8136.8 nM.

USE - (I) are useful for the treatment of pain, addictive disorder, Parkinson's diseases, anxiety and schizophrenia (claimed).

MC CPI: B06-H; B07-D10; B07-D11; B14-C01; B14-J01A3; B14-J01B3; B14-J01B4; B14-M01C

TECH

ORGANIC CHEMISTRY - Preparation: (I) where R2 is 1-10C alkyl is prepared by reacting 2-pyrimidinylpiperazine derivative of formula (A) with 1-10C alkyl iodide at low temperature in presence of lithium diisopropylamide optionally with hexamethylphosphoramide.

L20 ANSWER 2 OF 21 WPIX COPYRIGHT 2007 THE THOMSON CORP on STN

AN 2004-294977 [27] WPIX

DNC C2004-112814 [27]

TI New fused heterobicylco substituted phenyl derivatives are **metabotropic glutamate** receptor-subtype 5 modulators useful for the treatment or prevention of e.g. schizophrenia, anxiety and depression

DC B02
IN CAMPBELL B T; GUNZNER J L; MUNOZ B; STEARNS B A; VERNIER J A; VERNIER J M A; WANG B; GUNZER J L
PA (CAMP-I) CAMPBELL B T; (GUNZ-I) GUNZNER J L; (MERI-C) MERCK & CO INC; (MUNO-I) MUNOZ B; (STEA-I) STEARNS B A; (VERN-I) VERNIER J A; (WANG-I) WANG B
CYC 104
PI WO--2004024074 A2 20040325 (200427)* EN 37[0]
AU--2003267087 A1 20040430 (200462) EN
EP-----1539749 A2 20050615 (200539) EN
US-20050240021 A1 20051027 (200571) EN
JP--2006503038 W 20060126 (200609) JA 39
US-----7105533 B2 20060912 (200660) EN
ADT WO--2004024074 A2 2003WO-US0028344 20030909; US-20050240021 A1 Provisional **2002US-000410549P 20020913**; AU--2003267087 A1 2003AU-000267087 20030909; EP-----1539749 A2 2003EP-000749563 20030909; EP-----1539749 A2 2003WO-US0028344 20030909; US-20050240021 A1 2003WO-US0028344 20030909; JP--2006503038 W 2003WO-US0028344 20030909; JP--2006503038 W 2004JP-000536428 20030909; US-20050240021 A1 2005US-000527044 20050308; US-----7105533 B2 Provisional **2002US-000410549P 20020913**; US-----7105533 B2 2003WO-US0028344 20030909; US-----7105533 B2 2005US-000527044 20050308
FDT AU--2003267087 A1 Based on WO--2004024074 A; EP-----1539749 A2 Based on WO--2004024074 A; JP--2006503038 W Based on WO--2004024074 A; US-----7105533 B2 Based on WO--2004024074 A
PRAI **2002US-000410549P 20020913**
2005US-000527044 20050308
IPCI A61K-0031/4353 [I,C]; A61K-0031/4353 [I,C]; A61K-0031/437 [I,A]; A61K-0031/4375 [I,A]; A61K-0031/4427 [I,C]; A61K-0031/4439 [I,A]; A61K-0031/444 [I,A]; **A61K-0045/00** [I,A]; A61P-0021/00 [I,C]; A61P-0021/04 [I,A]; A61P-0025/00 [I,A]; A61P-0025/04 [I,A]; A61P-0025/08 [I,A]; A61P-0025/14 [I,A]; A61P-0025/16 [I,A]; **A61P-0025/18** [I,A]; A61P-0025/22 [I,A]; A61P-0025/24 [I,A]; A61P-0025/28 [I,A]; A61P-0025/30 [I,A]; A61P-0025/34 [I,A]; A61P-0029/00 [I,A]; A61P-0039/00 [I,C]; A61P-0039/02 [I,A]; A61P-0043/00 [I,A]; C07D-0401/00 [I,C]; C07D-0401/10 [I,A]; C07D-0471/00 [I,C]; C07D-0471/02 [I,A]; C07D-0471/04 [I,A]; C07D-0487/00 [I,C]; C07D-0487/02 [I,A]; C07D-0487/04 [I,A]; C07D-0513/00 [I,C]; C07D-0513/02 [I,A]; C07D-0513/04 [I,A]
IPCR A61K-0031/4738 [I,C]; A61K-0031/4745 [I,A]; C07D-0471/00 [I,C]; C07D-0471/00 [I,C]; C07D-0471/02 [I,A]; C07D-0471/04 [I,A]; C07D-0471/04 [I,A]
AB WO 2004024074 A2 UPAB: 20060919
NOVELTY - Fused heterobicyclo substituted phenyl derivatives (I) and their salts are new.

DETAILED DESCRIPTION - Fused heterobicyclo substituted phenyl derivatives (I) and their salts are new.

X1, X2, X4, X6 = C, N, S or O;
X3, X5 = C or N;
Y = 0-4C alkyl, aryl or heteroaryl;
Q = (CH2)n1
Q1 = (CH2)n2
R1, R2 = halo, 0-4C alkyl or pyridyl; and
n1, n2 = 0-1.

provided that at least one of X1, X2, X3, X4, X5 and X6 is N; at most one of X1, X2, X4 and X6 is S or O.

AN INDEPENDENT CLAIM is also included for a composition comprising (I).

ACTIVITY - Analgesic; Antiinflammatory; Tranquilizer; Antidepressant; Neuroleptic; Antiaddictive; Nootropic; Neuroprotective; Antiparkinsonian; Anticonvulsant; Muscular-Gen.; Eating-Disorders-Gen.

MECHANISM OF ACTION - **Metabotropic glutamate** receptor-subtype 5 (**mGluR5**) modulator. (I) were assessed for **mGluR5** modulatory activity using calcium flux assay in mouse fibroblast Ltk - cells (the **hmGluR5a**/L38 cell line). The median inhibitory concentration of 3-(3-methoxy-4-(pyridin-2-yl)phenyl)imidazo(1,5-a)pyridine hydrochloride was less than 5 muM.

USE - (I) are useful for the treatment or prevention of pain, pain disorders (preferably acute pain, persistent pain, chronic pain, inflammatory pain or neuropathic pain), anxiety, depression, bipolar disorders, psychosis, drug withdrawal, tobacco withdrawal, memory loss, cognitive impairment, dementia, Alzheimer's disease, schizophrenia, pain, disorders of extrapyramidal motor function (preferably Parkinson's disease, progression supramuscular palsy, Huntington's disease, Gille de la Tourette syndrome or tardive dyskinesia), anxiety disorders (preferably panic attack, agoraphobia or specific phobias, obsessive-compulsive disorders, post-traumatic stress disorder, acute stress disorder, generalized anxiety disorders, eating disorders, substance-induced anxiety disorder or nonspecified anxiety), epilepsy, cognitive dysfunction and drug addiction (claimed).

ADVANTAGE - (I) has minimum side effects.

MC CPI: B06-H; B10-A04; B10-A09B; B10-B02E; B10-B04B; B10-C04E; B14-C01; B14-E11; B14-E12; B14-J01; B14-J07; B14-M01C

TECH

ORGANIC CHEMISTRY - Preparation: No general preparation is given.
PHARMACEUTICALS - Preferred Composition: Composition of (I) further comprises opiate agonist, opiate antagonist, calcium channel antagonist, 5-hydroxytryptamine (5-HT) receptor agonist, 5-HT receptor antagonist, sodium channel antagonist, N-methyl-d-aspartate receptor agonist, NMDA receptor antagonist, cycloxygenase-2 selective inhibitor, NK1 antagonist, non-steroidal anti-inflammatory drug, gamma amino butyric acid -A receptor modulator, dopamine agonist, dopamine antagonist, selective serotonin reuptake inhibitor, tricyclic antidepressant drug, a norepinephrine modulator, L-3,4-dihydroxyphenyl alanine, buspirone, lithium salt, valproate, neurontin, **olanzapine**, nicotinic agonist, a nicotinic antagonist, muscarinic antagonist, selective serotonin and norepinephrine reuptake inhibitor, heroin substituting drug (preferably methadone, levo-alpha-acetylmethadol, buprenorphine or naltrexone), disulfiram or acamprosate.

L20 ANSWER 3 OF 21 WPIX COPYRIGHT 2007 THE THOMSON CORP on STN
AN 2004-214483 [20] WPIX
DNC C2004-084975 [20]
TI Treatment of schizophrenia with **mGluR1** antagonist, especially a thiazolo(3,2-a)benzimidazole-2-carboxamide or its derivative
DC B02
IN MITSUYA M; OHKUBO M; OHTA H; SATO A; TANAKA T; TSUKAMOTO N
PA (BANY-C) BANYU PHARM CO LTD
CYC 103
PI WO--2004016287 A1 20040226 (200420)* JA 52[0]
AU--2003255022 A1 20040303 (200457) EN
ADT WO--2004016287 A1 2003WO-JP0010286 20030813; AU--2003255022 A1 2003AU-000255022 20030813
FDT AU--2003255022 A1 Based on WO--2004016287 A
PRAI **2002JP-000236267 20020814**
IPCR A61K-0031/429 [I,A]; A61K-0031/429 [I,C]; A61P-0025/00 [I,C]; **A61P-0025/18** [I,A]; A61P-0043/00 [I,A]; A61P-0043/00 [I,C]; C07D-0513/00 [I,C]; C07D-0513/04 [I,A]
AB WO 2004016287 A1 UPAB: 20050528
NOVELTY - Treatment agent for schizophrenia contains a **mGluR1** antagonist compound or its salt.

ACTIVITY - Neuroleptic.

MECHANISM OF ACTION - **mGlu**-Antagonist-R1.

Mice were used in model animal studies of schizophrenia. The mice were treated with methamphetamine (MAP), and movements were recorded for a fixed period. The **mGluR1** antagonist compound 6-amino-N-cyclohexyl-N,3-dimethylthiazolo(3,2- a)benzimidazole-2-carboxamide (Ia) (10 mg/kg) was given subcutaneously, 30 minutes before the methamphetamine. Number of movements was about 1300 when no MAP and no (Ia) was given; about 1200 when only (Ia) was given; about 2400 when only MAP was given; and about 900 when both MAP and (Ia) were given.

USE - (I) is used to treat schizophrenia.

MC CPI: B06-F03; B06-F05; B14-J01B3

TECH
PHARMACEUTICALS - Preferred compound: The **mGluR1** antagonist is a thiazoloimidazole compound of formula (I).
R1 = -A1-CO-NR5R6, -A1-CO-A2-R7, -A1-CO-A3-NR5R6, -A1-O-A2- R8, -A1-R8, -A1-NR5R6, -A1-NR5-CO-R6, or NR9-COOR10, (especially CONRaRb or CH2NRaRb);
A1 = bond, or lower alkylene (optionally substituted by hydroxy);
A2 = bond, lower alkylene or lower alkenylene;
A3 = lower alkylene (optionally substituted by hydroxy);
R2 = H, or lower alkyl (optionally substituted by halo, hydroxy, lower alkoxy, amino, or mono- or di-lower alkylamino);
R3, R4 = H, halo, nitro, optionally substituted lower alkyl, optionally substituted aryl, optionally substituted heteroaryl, COR11, lower alkoxycarbonylamino, -C(R14)=CR12R13 or -C(R14)(R12a)C(=CH2)-R13; or
R3+R4 = group completing an optionally substituted carbocyclic ring (optionally containing 1 or 2 double bonds) or optionally substituted 1-3C heteroaryl ring, especially optionally substituted benzene;
dashed line = optional bond;
R5, R6 = H, NR19R20, optionally substituted hydrocarbyl or optionally substituted heterocyclyl; or
NR5R6 = optionally substituted heterocyclyl, optionally containing other heteroatom(s);
R7 = H, optionally substituted hydrocarbyl, optionally substituted heterocyclyl, hydroxy or lower alkoxy;
R8 = H, optionally substituted hydrocarbyl or optionally substituted heterocyclyl;
R9 = H or lower alkyl;
R10 = optionally substituted hydrocarbyl or optionally substituted heterocyclyl;
R11 = H, hydroxy or saturated heterocyclyl;
R12, R13 = H, optionally substituted lower alkyl, optionally substituted aryl, optionally substituted heteroaryl, lower alkoxycarbonyl or COR15; or
CR12R13 = cycloalkyl or saturated heterocyclyl;
R12a = NR16R17;
R15 = H, hydroxy or saturated heterocyclyl;
R16-R18 = H or lower alkyl; or NR16R17 = heteroaryl or heterocyclyl (both optionally substituted and both optionally containing other heteroatom(s));
R19, R20 = H, lower alkylcarbonyl, lower haloalkylcarbonyl or COOR18;
Ra, Rb = H, lower alkyl or cycloalkyl.

L20 ANSWER 4 OF 21 WPIX COPYRIGHT 2007 THE THOMSON CORP on STN
AN 2004-191072 [18] WPIX
DNC C2004-075303 [18]
TI Use of 6H-pyrrolo(3,4-D)pyridazine compounds as binder of the alpha-2-delta subunit of voltage gated calcium channels for treating e.g. bipolar disorder, dementia, epilepsy, cognitive dysfunction
DC B02
IN ANKER N B; ARRUDA J M; CAMPBELL B T; MUNOZ B; PRASIT P; STEARNS B A; HU T
PA (MERI-C) MERCK & CO INC; (ANKE-I) ANKER N B; (ARRU-I) ARRUDA J M; (CAMP-I) CAMPBELL B T; (HUTT-I) HU T; (MUNO-I) MUNOZ B; (PRAS-I) PRASIT P; (STEA-I) STEARNS B A
CYC 103
PI WO--2004006836 A2 20040122 (200418)* EN 203[0]
AU--2003248907 A1 20040202 (200450) EN
EP-----1539168 A2 20050615 (200539) EN
JP--2005536507 W 20051202 (200582) JA 194
US-20060154929 A1 20060713 (200646) EN
ADT WO--2004006836 A2 2003WO-US0021493 20030708; AU--2003248907 A1 2003AU-000248907 20030708; EP-----1539168 A2 2003EP-000764414 20030708; EP-----1539168 A2 2003WO-US0021493 20030708; JP--2005536507 W 2003WO-US0021493 20030708; JP--2005536507 W 2004JP-000521592 20030708; US-20060154929 A1 Provisional **2002US-000394734P 20020711**; US-20060154929 A1 2003WO-US0021493 20030708; US-20060154929 A1 2005US-000520962 20051128
FDT AU--2003248907 A1 Based on WO--2004006836 A; EP-----1539168 A2 Based on WO--2004006836 A; JP--2005536507 W Based on WO--2004006836 A

PRAI **2002US-000394734P 20020711**
2005US-000520962 20051128
IC ICM A61K-031/5025
IPCI A61K-0031/503 [I,A]; A61K-0031/503 [I,C]
IPCR A61K-0031/045 [I,A]; A61K-0031/045 [I,C]; A61K-0031/05 [I,A]; A61K-0031/435 [I,A]; A61K-0031/435 [I,C]; A61K-0031/495 [I,A]; A61K-0031/495 [I,C]; A61K-0031/50 [I,A]; A61K-0031/50 [I,C]; A61K-0031/5025 [I,A]; A61K-0031/5025 [I,C]; A61K-0031/5375 [I,C]; A61K-0031/5377 [I,A]; A61K-0031/55 [I,A]; A61K-0031/55 [I,C]; A61K-0031/551 [I,A]; A61K-0031/551 [I,C]; A61K-0031/553 [I,A]; A61K-0031/553 [I,C]; A61P-0017/00 [I,C]; A61P-0017/06 [I,A]; A61P-0025/00 [I,C]; A61P-0025/04 [I,A]; A61P-0025/08 [I,A]; A61P-0025/14 [I,A]; A61P-0025/16 [I,A]; A61P-0025/20 [I,A]; A61P-0025/22 [I,A]; A61P-0025/24 [I,A]; A61P-0025/28 [I,A]; A61P-0039/00 [I,C]; A61P-0039/02 [I,A]; C07D-0487/00 [I,C]; C07D-0487/04 [I,A]; C07D-0519/00 [I,A]; C07D-0519/00 [I,C]
AB WO 2004006836 A2 UPAB: 20060203
NOVELTY - Binding the alpha-2-delta subunit of voltage gated calcium channels involves administration of 6H-pyrrolo(3,4-D)pyridazine compounds.

DETAILED DESCRIPTION - Binding the alpha-2-delta subunit of voltage gated calcium channels involves administration of 6H-pyrrolo(3,4-D)pyridazine compounds of formula (I) (excluding compounds of formulae (Ia), (Ib)) or their salts).

R1 = 0-6C alkyl-aryl, 0-6C alkyl-heteroaryl, 0-6C alkyl-(3-6C cycloalkyl) or 0-6C alkyl-hetero-3-7C cycloalkyl (all optionally substituted by T1, 0-6C alkyl-(3-6C cycloalkyl) or 0-6C alkyl-hetero-3-7C cycloalkyl);

T1 = halo, -CN, NO2, 1-6C alkyl, OR6, NR6R7, -C(=NR6)NR7R8, -N(-R88R6)NR7R8, -NR6COR7, -NR6CO2R7, -NR6SO2R88, -NR6CONR7R8, -SR88, -SOR88, -SO2R88, -SO2NR6R7, -COR6, -CO2R6, -CONR6R7, -C(=NR6)R7 or -C(=NOR6)R7;

R2-R5 = 0-6C alkyl, 0-6C alkyl-aryl, 0-6C alkyl-heteroaryl, 0-6C alkyl-(3-6C cycloalkyl) or 0-6C alkyl-hetero-3-7C cycloalkyl (all optionally substituted by T1); and

R6-R8 and R88 = 0-6C alkyl, 3-7C cycloalkyl or (hetero)aryl (all optionally mono- to penta-substituted by halo, CN, 1-6C alkyl, O(0-6C alkyl), O(3-7C cycloalkyl), -O(aryl), -N(0-6C alkyl)(0-6C alkyl), -N(0-6C alkyl)(3-7C cycloalkyl) or -N(0-6C alkyl)(aryl));

T2 = 4-ethoxy-benzene-1-yl; and

T3 = 4-hydroxy phenyl, 4-aminophenyl, 4-chlorophenyl, 4-piperidin-1-yl phenyl, 3-amino-4-methyl-phenyl, 4-diethylamino phenyl, phenyl, 2-aminophenyl, 4-bromophenyl, 3,4-dimethylphenyl, 3-ethoxyphenyl, or 4-fluorophenyl.

INDEPENDENT CLAIMS are included for the following:

(a) the treatment of neuropathic pain involving administration of a composition (C1) comprising (I) and carrier; and

(b) new 6H-pyrrolo(3,4-D)pyridazine compounds (excluding 69 compounds as given in the specification e.g. 6-methyl-6H-pyrrolo(3,4-d)pyridazine, 1-ethoxy-2,5,6,7-tetramethyl-6H-pyrrolo(3,4-d)pyridazinium tetrafluoroborate and 6-(4-ethoxy-phenyl)-5,7-dimethyl-6H-pyrrolo(3,4-d)pyridazine) or its salt.

ACTIVITY - Analgesic; Tranquilizer; Eating-Disorder-Gen.; Antidepressant; Neuroleptic; Antiaddictive; Antismoking; Nootropic; Neuroprotective; Antiparkinsonian; Anticonvulsant; Muscular-Gen.; CNS-Gen.; Hypnotic.

The analgesic efficacy of 6-(4-ethoxyphenyl)-1,4,5,7-tetramethyl-6H-pyrrolo(3,4-d)pyridazine (A1) was evaluated on nerve injury-induced tactile allodynia by spinal nerve ligation model of neuropathic pain. Male Sprague Dawley rats were tested for tactile allodynia by applying a series of calibrated von Frey filaments to the plantar aspect of the left hindpaw ipsilateral to the site of nerve injury. (A1) Was administered intraperitoneally and wind paw withdrawal threshold was measured. (A1) showed 100% protective effect at dosage of 20 mg/kg.

MECHANISM OF ACTION - Voltage gated calcium channel alpha-2delta subunit binder.

(I) Were tested for binding specificity to alpha-2-delta subunit of

voltage gated calcium channels by competitive binding assay using membranes from A710 (HEK293 cells co-expressing alpha1b, alpha2delta, beta3). The membranes were incubated with (3H)-GABA pentin (7 nM) at room temperature for 1 hour, in presence of (I). From competitive binding analysis, (I) showed IC50 of less than 10 microM.

USE - For treating pain disorder (e.g. acute, persistent, chronic, inflammatory, and neuropathic pain), anxiety disorder (e.g. panic attack, agoraphobia or specific phobias, obsessive-compulsive disorders, post-traumatic stress disorder, acute stress disorder, generalized anxiety disorder, eating disorder, substance-induced anxiety disorder, or nonspecified anxiety disorder), depression, bipolar disorder, psychosis, drug withdrawal, tobacco withdrawal, memory loss, cognitive impairment, dementia, Alzheimer's disease, schizophrenia, panic, disorders of extrapyramidal motor function (e.g. Parkinson's disease, progressive supramuscular palsy, Huntington's disease, Gilles de la Tourette syndrome, or tardive dyskinesia), epilepsy, cognitive dysfunction, drug addiction, drug abuse, drug withdrawal, circadian rhythm and sleep disorders (e.g. shift-work induced sleep disorder or jet-lag) (claimed).

ADVANTAGE - The compounds have high-affinity binding to alpha-2-delta subunit of voltage gated calcium channels.

MC CPI: B04-A04; B06-D08; B06-F05; B07-D05; B10-A04; B10-A09B; B10-B02B; B10-B02E; B10-B04B; B10-C04E; B14-C01; B14-C03; B14-D05C; B14-J01; B14-J02; B14-J04; B14-J05; B14-J07; B14-L01; B14-L06; B14-M01B; B14-M01C

TECH

ORGANIC CHEMISTRY - Preparation: No general method for preparation of (I) (excluding 69 compounds as given in the specification e.g. 6-methyl-6H-pyrrolo(3,4-d)pyridazine, 1-ethoxy-2,5,6,7-tetramethyl-6H-pyrrolo(3,4-d)pyridazinium tetrafluoroborate and 6-(4-ethoxy-phenyl)-5,7-dimethyl-6H-pyrrolo(3,4-d)pyridazine) is given.

PHARMACEUTICALS - Preferred Method: The composition further comprises opiate agonist, opiate antagonist, **metabotropic glutamate** receptor 5 (**mGluR5**) antagonist, 5-hydroxytryptamine(HT) receptor agonist, 5HT receptor antagonist, sodium channel antagonist, N-methyl-D-aspartase (NMDA) receptor agonist, NMDA receptor antagonist, cyclooxygenase-2 selective inhibitor, Neurokinin-1 antagonist, non-steroidal anti-inflammatory drug, gamma-aminobutyric acid-A receptor modulator, dopamine agonist, dopamine antagonist, selective serotonin reuptake inhibitor, tricyclic antidepressant drug, norepinephrine modulator, L-dihydroxyphenylalanine (L-DOPA), buspirone, lithium salt, valproate, neurontin, **olanzapine**, nicotinic agonist, nicotinic antagonist, muscarinic agonist, muscarinic antagonist, selective serotonin and norepinephrine reuptake inhibitor (SSNRI), heroin substituting drug (e.g. methadone, levo-alpha-acetylmethadol, buprenorphine or naltrexone), disulfiram or acamprosate.

L20 ANSWER 5 OF 21 WPIX COPYRIGHT 2007 THE THOMSON CORP on STN
AN 2003-788196 [74] WPIX
DNC C2003-217616 [74]
TI New di-aryl substituted tetrazole compounds useful for treating and preventing e.g. pain disorder, anxiety disorder and depression
DC B02; B03; C02
IN CHEN C; COSFORD N D P; EASTMAN B W; HUANG D; POON S F; REGER T R; REGER T S; ROPPE J R; SMITH N D
PA (CHEN-I) CHEN C; (COSF-I) COSFORD N D P; (EAST-I) EASTMAN B W; (HUAN-I) HUANG D; (MERI-C) MERCK & CO INC; (POON-I) POON S F; (REGE-I) REGER T S; (ROPP-I) ROPPE J R; (SMIT-I) SMITH N D
CYC 101
PI WO--2003077918 A1 20030925 (200374)* EN 85[0]
AU--2003213783 A1 20030929 (200432) EN
EP-----1485093 A1 20041215 (200482) EN
US-20050153986 A1 20050714 (200547) EN
JP--2005526081 W 20050902 (200559) JA 159
AU--2003213783 B2 20070125 (200731) EN
ADT WO--2003077918 A1 2003WO-US0007074 20030307; US-20050153986 A1 Provisional **2002US-000363456P 20020312**; AU--2003213783 A1

2003AU-000213783 20030307; EP-----1485093 A1 2003EP-000711474 20030307; JP--2005526081 W 2003JP-000575971 20030307; EP-----1485093 A1 2003WO-US0007074 20030307; US-20050153986 A1 2003WO-US0007074 20030307; JP--2005526081 W 2003WO-US0007074 20030307; US-20050153986 A1 2004US-000506479 20040901; AU--2003213783 B2 2003AU-000213783 20030307

FDT AU--2003213783 A1 Based on WO--2003077918 A; EP-----1485093 A1 Based on WO--2003077918 A; JP--2005526081 W Based on WO--2003077918 A; AU--2003213783 B2 Based on WO--2003077918 A

PRAI **2002US-000363456P 20020312**
2004US-000506479 20040901

IC ICM C07D-401/04
ICS A61K-031/4439; A61K-031/4709; A61K-031/506; A61K-031/5377; A61P-025/00; A61P-025/04; **A61P-025/18**; A61P-025/22; A61P-025/24; A61P-025/28; A61P-025/34; C07D-401/14; C07D-405/14; C07D-409/14; C07D-413/14; C07D-417/14; C07D-471/04

IPCI A61K-0031/4427 [I,C]; A61K-0031/4439 [I,A]; A61K-0031/4709 [I,A]; A61K-0031/4709 [I,C]; A61K-0031/506 [I,A]; A61K-0031/506 [I,C]; A61K-0031/5375 [I,C]; A61K-0031/5377 [I,A]; A61P-0025/00 [I,A]; A61P-0025/00 [I,C]; A61P-0025/04 [I,A]; **A61P-0025/18** [I,A]; A61P-0025/22 [I,A]; A61P-0025/24 [I,A]; A61P-0025/28 [I,A]; A61P-0025/34 [I,A]; C07D-0401/00 [I,C]; C07D-0401/04 [I,A]; C07D-0401/14 [I,A]; C07D-0405/00 [I,C]; C07D-0405/14 [I,A]; C07D-0409/00 [I,C]; C07D-0409/14 [I,A]; C07D-0413/00 [I,C]; C07D-0413/14 [I,A]; C07D-0417/00 [I,C]; C07D-0417/14 [I,A]; C07D-0471/00 [I,C]; C07D-0471/04 [I,A]

IPCR A61K-0031/4427 [I,C]; A61K-0031/4439 [I,A]; A61K-0031/444 [I,A]; A61K-0031/4709 [I,A]; A61K-0031/4709 [I,C]; A61K-0031/506 [I,A]; A61K-0031/506 [I,A]; A61K-0031/506 [I,C]; A61K-0031/506 [I,C]; A61K-0031/5375 [I,C]; A61K-0031/5377 [I,A]; A61P-0025/00 [I,A]; A61P-0025/00 [I,C]; A61P-0025/04 [I,A]; **A61P-0025/18** [I,A]; A61P-0025/22 [I,A]; A61P-0025/24 [I,A]; A61P-0025/28 [I,A]; A61P-0025/34 [I,A]; C07D-0401/00 [I,C]; C07D-0401/04 [I,A]; C07D-0401/14 [I,A]; C07D-0405/00 [I,C]; C07D-0405/14 [I,A]; C07D-0409/00 [I,C]; C07D-0409/14 [I,A]; C07D-0413/00 [I,C]; C07D-0413/14 [I,A]; C07D-0417/00 [I,C]; C07D-0417/14 [I,A]; C07D-0471/00 [I,C]; C07D-0471/04 [I,A]

AB WO 2003077918 A1 UPAB: 20060120

NOVELTY - Di-aryl substituted tetrazole compounds (I) are new.

DETAILED DESCRIPTION - Di-aryl substituted tetrazole compounds of formula (I) or its salts are new.

X = (hetero)aryl (optionally mono- to hepta-substituted by T (where optionally two substituents are combined to form (hetero)cycloalkyl ring fused to X, and -1-6C alkyl and (hetero)cycloalkyl are both optionally mono- to penta-substituted by T1));

T = halo, -CN, NO2, -1-6C alkyl, -1-6C alkenyl, -1-6C alkynyl, -OR1, -NR1R2, -C(=NR1)NR2R3, -N(=NR1)NR2R3, -NR1COR2, -NR1CO2R2, -NR1SO2R4, -NR1CONR2R3, -SR4, -SOR4, -SO2R4, -SO2NR1R2, -COR1, -CO2R1, -CONR1R2, -C(=NR1)R2 or -C(=NOR1)R2;

T1 = halo, -CN, -1-6C alkyl, -O(0-6C alkyl), -O(3-7C cycloalkyl), -O(aryl), -N(0-6C alkyl)(0-6C alkyl), -N(0-6C alkyl)(3-7C cycloalkyl), or -N(0-6C alkyl)(aryl);

Y' = (hetero)aryl (optionally mono- to hepta-substituted by halo, -CN, NO2, -1-6C alkyl, -1-6C alkenyl, -1-6C alkynyl, -OR5, -NR5R6, -C(=NR5)NR6R7, -N(=NR5)NR6R7, -NR5COR6, -NR5CO2R6, -NR5SO2R8, -NR5CONR6R7, -SR8, -SOR8, -SO2R8, -SO2NR5R6, -COR5, -CO2R5, -CONR5R6, -C(=NR5)R6 or -C(=NOR5)R6 (where optionally two substituents are combined to form (hetero)cycloalkyl ring fused to Y', and -1-6C alkyl and (hetero)cycloalkyl are both optionally mono- to penta-substituted by T1));

R1 - R3, R5 - R7, R9, R10 = 0-6C alkyl, 3-7C cycloalkyl, or (hetero)aryl (all optionally mono- to penta-substituted by T1);

R4, R8 = 1-6C alkyl, -3-7C cycloalkyl, or (hetero)aryl (all optionally mono- to penta-substituted by T1);

A = 0-4C alkyl, 0-2C alkyl-SO-0-2C alkyl-, 0-2C alkyl-SO20-2C alkyl-, 0-2C alkyl-CO-0-2C alkyl-, 0-2C alkyl-NR9CO-0-2C alkyl-, 0-2C alkylNR9SO2-0-2C alkyl- or hetero-0-4C alkyl;

W', Z' = 3-7C cycloalkyl, hetero-3-7C cycloalkyl, 0-6C alkylaryl, or 0-6C alkylheteroaryl (all optionally mono- to hepta-substituted by T);

B' = 0-4C alkyl, 0-2C alkyl-SO-0-2C alkyl-, 0-2C alkyl-SO2-0-2C

alkyl-, 0-2C alkyl-CO-0-2C alkyl-, 0-2C alkyl-NR10CO-0-2C alkyl-, 0-2C alkylNR10SO2-0-2C alkyl- or hetero-1-4C alkyl.

Provided that: at least one of X and Y is a heteroaryl with N adjacent to the position of attachment to A or B respectively; one of W and Z is optionally absent; and any N may be an N-oxide.

An INDEPENDENT CLAIM is included for a pharmaceutical composition comprising (I) and a carrier.

ACTIVITY - Analgesic; Antiinflammatory; Tranquilizer; Eating-Disorder-Gen.; Antidepressant; Neuroleptic; Nootropic; Antiaddictive; Antismoking; Neuroprotective; Antiparkinsonian; Anticonvulsant; Muscular-Gen.; CNS-Gen.; Hypnotic; Anorectic.

MECHANISM OF ACTION - **Metabotropic glutamate** receptor-5 modulator.

(I) was tested for **metabotropic glutamate** receptor-5 inhibitory activity and IC50 was found to be at most 10 microM and at most 100 microM in the calcium flux assay and PI assay, respectively. No specific result for specific compound given.

USE - For treating and preventing pain disorder (e.g. acute pain, chronic pain, inflammatory pain or neuropathic pain), anxiety disorder (e.g. panic attack, agoraphobia or specific phobias, obsessive-compulsive disorders, post-traumatic stress disorder, acute stress disorder, generalized anxiety disorder, eating disorder, substance-induced anxiety disorder or nonspecific anxiety disorder), depression, bipolar disorder, psychosis, drug withdrawal, tobacco withdrawal, memory loss, cognitive impairment, dementia, Alzheimer's disease, schizophrenia, panic, extrapyramidal motor function disorder (e.g. Parkinson's disease, progressive supramuscular palsy, Huntington's disease, Gilles de la Tourette syndrome or tardive dyskinesia), epilepsy, circadian rhythm, sleep disorder (e.g. shift-work induced sleep disorder or jet-lag) and obesity.

ADVANTAGE - The compound inhibits **metabotropic glutamate** receptor-5 with minimal side effects.

MC CPI: B05-A01B; B06-A02; B06-B02; B06-E05; B06-F05; B07-D04; B07-D05; B07-D11; B07-D12; B07-D13; B07-F01; B07-H; B10-A04; B10-B04B; B10-C04E; B14-C01; B14-C03; B14-E11; B14-E12; B14-J01; B14-J01A1; B14-J01A3; B14-J01A4; B14-J01B1; B14-J01B2; B14-J01B3; B14-J01B4; B14-J05; B14-J07; B14-M01B; B14-M01C; C05-A01B; C06-A02; C06-B02; C06-E05; C06-F05; C07-D04; C07-D05; C07-D11; C07-D12; C07-D13; C07-F01; C07-H; C14-C01; C14-C03; C14-E11; C14-E12; C14-J01A1; C14-J01A3; C14-J01A4; C14-J01B1; C14-J01B2; C14-J01B3; C14-J01B4; C14-J05; C14-J07; C14-M01B; C14-M01C

TECH

ORGANIC CHEMISTRY - Preparation: Preparation of (I) (where A, B, W and Z are absent) involves:
(1) reacting a ring system of formula Y-C(O)-H (i) (where Y contains an aldehyde moiety) with an arylsulfonylhydrazide in a solvent (e.g. tetrahydrofuran or dimethylformamide) at 0 - 100 degrees C for 5 - 60 minutes to form an arylsulfonylhydrazone of formula Y-CH=N-NH-SO2-Ar (ii);
(2) reacting an amine-substituted compound of formula X-N+equivalent to N (iii) with nitrous acid at -10 - 0 degrees C in a solvent (e.g. water) to obtain an arenediazonium species (A); and
(3) reacting (ii) with (A) in a 1,3-dipolar cycloaddition reaction.
PHARMACEUTICALS - Preferred Composition: The composition additionally comprises an opiate agonist, opiate antagonist, calcium channel antagonist, 5HT receptor agonist, 5HT receptor antagonist, sodium channel antagonist, N-methyl-D-aspartate (NMDA) receptor agonist, NMDA receptor antagonist, cyclooxygenase (COX)-2 selective inhibitor, NK1 antagonist, non-steroidal anti-inflammatory drug, gamma amino butyric acid (GABA)-A receptor modulator, dopamine agonist, dopamine antagonist, selective serotonin reuptake inhibitor, tricyclic antidepressant drug, norepinephrine modulator, L-dihydroxyphenylalanine (DOPA), buspirone, lithium salt, valproate, neurontin, **olanzapine**, nicotinic agonist, nicotinic antagonist, muscarinic agonist, muscarinic antagonist, selective serotonin and norepinephrine reuptake inhibitor (SSNRI), heroin substituting drug (e.g. methadone, levo-alpha-acetylmethadol, buprenorphine, or naltrexone), disulfiram or acamprosate.

L20 ANSWER 6 OF 21 WPIX COPYRIGHT 2007 THE THOMSON CORP on STN
AN 2003-697431 [66] WPIX
DNC C2003-191725 [66]
TI New pyridylpiperazine compounds are **metabotropic glutamate** receptor inhibitors, useful for the treatment of pain, urinary incontinence, ulcer inflammatory bowel disease, Parkinson's disease
DC B02; B03
IN KYLE D J; QUN S; SUN Q
PA (EURO-N) EUROCELTIQUE SA; (KYLE-I) KYLE D J; (QUNS-I) QUN S
CYC 101
PI WO--2003066595 A2 20030814 (200366)* EN 80[0]
US-20040044003 A1 20040304 (200417) EN
AU--2003212882 A1 20030902 (200425) EN
EP-----1472225 A2 20041103 (200472) EN
JP--2005521679 W 20050721 (200549) JA 126
AU--2003212882 A8 20051027 (200624) EN
US-----7071335 B2 20060704 (200644) EN
US-20060148814 A1 20060706 (200645) EN
ADT WO--2003066595 A2 2003WO-US0002983 20030131; US-20040044003 A1 Provisional **2002US-000352855P 20020201**; US-----7071335 B2 Provisional **2002US-000352855P 20020201**; US-20040044003 A1 Provisional **2002US-000411043P 20020917**; US-----7071335 B2 Provisional **2002US-000411043P 20020917**; AU--2003212882 A1 2003AU-000212882 20030131; AU--2003212882 A8 2003AU-000212882 20030131; EP-----1472225 A2 2003EP-000708924 20030131; JP--2005521679 W 2003JP-000565969 20030131; US-20040044003 A1 2003US-000355186 20030131; US-----7071335 B2 2003US-000355186 20030131; EP-----1472225 A2 2003WO-US0002983 20030131; JP--2005521679 W 2003WO-US0002983 20030131; US-20060148814 A1 Provisional **2002US-000352855P 20020201**; US-20060148814 A1 Provisional **2002US-000411043P 20020917**; US-20060148814 A1 Cont of 2003US-000355186 20030131; US-20060148814 A1 2006US-000368133 20060302
FDT AU--2003212882 A1 Based on WO--2003066595 A; EP-----1472225 A2 Based on WO--2003066595 A; JP--2005521679 W Based on WO--2003066595 A; AU--2003212882 A8 Based on WO--2003066595 A
PRAI **2002US-000411043P 20020917**
2002US-000352855P 20020201
2003US-000355186 20030131
2006US-000368133 20060302
IC ICM C07D-213/74
ICS A61K-031/44
IPCI A61K-0031/496 [I,A]; A61K-0031/496 [I,A]; A61K-0031/496 [I,C]; C07D-0401/00 [I,C]; C07D-0401/04 [I,A]; C07D-0403/00 [I,C]; C07D-0403/02 [I,A]
IPCR A61K-0031/4965 [I,C]; A61K-0031/497 [I,A]; **A61K-0045/00** [I,A]; **A61K-0045/00** [I,C]; A61P-0001/00 [I,C]; A61P-0001/04 [I,A]; A61P-0001/08 [I,A]; A61P-0013/00 [I,C]; A61P-0013/02 [I,A]; A61P-0017/00 [I,C]; A61P-0017/04 [I,A]; A61P-0021/00 [I,A]; A61P-0021/00 [I,C]; A61P-0023/00 [I,A]; A61P-0023/00 [I,C]; A61P-0025/00 [I,A]; A61P-0025/00 [I,C]; A61P-0025/04 [I,A]; A61P-0025/08 [I,A]; A61P-0025/14 [I,A]; A61P-0025/16 [I,A]; **A61P-0025/18** [I,A]; A61P-0025/22 [I,A]; A61P-0025/24 [I,A]; A61P-0025/28 [I,A]; A61P-0025/30 [I,A]; A61P-0027/00 [I,C]; A61P-0027/02 [I,A]; A61P-0043/00 [I,A]; A61P-0043/00 [I,C]; A61P-0009/00 [I,C]; A61P-0009/10 [I,A]; C07D-0213/00 [I,C]; C07D-0213/74 [I,A]; C07D-0401/00 [I,C]; C07D-0401/04 [I,A]; C07D-0405/00 [I,C]; C07D-0405/12 [I,A]; C07D-0417/00 [I,C]; C07D-0417/12 [I,A]
AB WO 2003066595 A2 UPAB: 20060120
NOVELTY - Pyridylpiperazine compounds (I)-(III) are new.
DETAILED DESCRIPTION - Pyridylpiperazine compounds of formula (I)-(III) and their salts are new.
R1 = Me or halo;
R2 = 2-6C alkyl, 2-3C alkenyl, -(CH2)nC(O)R5, -(CH2)nOR5 or (CH2)nSR5 (optionally substituted by at least 1 Q1), Me, CH2F or CHF2 (optionally substituted by at least 1 CN, OH, Cl, Br, I, NO2, CH=NR5 or

NR5OH), H, halo, NO2, CN or NH2;
Q1 = CN, OH, halo, NO2, CH=NR5 or NR5OH;
R3 = 1-6C alkyl, 2-6C alkenyl, 2-6C alkynyl, (CH2)nOR5 (optionally substituted by at least 1 Q1), H, halo, NO2, CN or NH2;
R4 = 2-6C alkenyl, 2-6C alkynyl or Q2;
Q2 = 3-8C cycloalkyl, 5-8C cycloalkenyl, 6C aryl, 10C aryl, 14C aryl, 3-7C heterocycle, 1-6C alkyl-6C aryl, 1-6C alkyl-10C aryl, 1-6C alkyl-14C aryl, 1-6C alkyl-3-7C heterocycle, 2-6C alkenyl-6C aryl, 2-6C alkenyl-10C aryl, 2-6C alkenyl-14C aryl, 2-6C alkenyl-3-7C heterocycle, 2-6C alkynyl-3-8C cycloalkyl, 2-6C alkynyl-5-8C cycloalkenyl, 2-6C alkynyl-6C aryl, 2-6C alkynyl-10C aryl, 2-6C alkynyl-14C aryl or 2-6C alkynyl-3-7C heterocycle (optionally substituted by at least 1 R6);
R5 = H, 1-6C alkyl, 2-6C alkenyl, 2-6C alkynyl, 3-8C cycloalkyl, 5-8C cycloalkenyl, 6C aryl, 3-5C heterocycle, dihalomethyl or trihalomethyl;
R6 = 1-6C alkyl, 2-6C alkenyl, 2-6C alkynyl, -(CH2)n-3-8C cycloalkyl, -(CH2)n-5-8C cycloalkenyl, -(CH2)n-6C aryl, (CH2)nSR5, (CH2)nCH(halo)2, (CH2)nC(halo)3, halo or -(CH2)nOR5;
n, p = 0-2;
X = O or S;
Ar = 6C aryl, 10C aryl, 14C aryl, 3-8C cycloalkyl or 5-8C cycloalkenyl (optionally substituted by at least 1 R6);
R4a = 1-6C alkyl, 2-6C alkenyl, 2-6C alkynyl, (CH2)n-3-8C cycloalkyl, -(CH2)n-5-8C cycloalkenyl, (CH2)n-6C aryl, (CH2)nSR5a, (CH2)nCH(halo)2, (CH2)nC(halo)3, halo or (CH2)nOR5a;
R5a = 1-6C alkyl, 2-6C alkenyl, 2-6C alkynyl or aryl;
R1a = H, halo, 1-6C alkyl, NO2, CN, OH, OCH3, C(halo)3, CH(halo)2 or CH2(halo);
R4b = 1-6C alkyl, 2-6C alkenyl, 2-6C alkynyl, (CH2)n-3-8C cycloalkyl, -(CH2)n-5-8C cycloalkenyl, (CH2)n-6C aryl, (CH2)nSR5b, (CH2)nCH(halo)2, (CH2)nC(halo)3, halo or (CH2)nOR5b;
R5b = alkyl, alkenyl, alkynyl or aryl.
ACTIVITY - Analgesic; Antidepressant; Tranquilizer; Uropathic; Antiulcer; Antiinflammatory; Gastrointestinal-Gen.; Antiaddictive; Antiparkinsonian; Anticonvulsant; Cerebroprotective; Antipruritic; Neuroleptic; Nootropic; Neuroprotective; Ophthalmological; Relaxant; Antimigraine; Antiemetic; Muscular-Gen.
MECHANISM OF ACTION - **Metabotropic Glutamate** Receptor-5 (**mGluR5**) Inhibitor, **mGluR1** Inhibitor; Vanilloid Receptor-1 (VR-1) Inhibitor.
In a fluorometric assay using Chinese hamster ovary (CHO)-rat **mGluR5** cells, 4-(3-chloro-pyridin-2-yl)-2-methyl-piperazine-1-carboxylic acid (2-(2,3-dimethyl-phenyl)-ethyl)-amide (Ia) inhibited **mGlu**-5 receptors with an IC50 of 10 microM.
USE - For the treatment of pain, depression and anxiety (claimed), urinary incontinence, ulcer, inflammatory bowel disease, irritable bowel syndrome, addictive disorders, Parkinson's disease, parkinsonism, epilepsy, stroke, seizure, pruritic condition, psychosis, cognitive disorder, memory deficit, restricted brain function, Huntington's chorea, amyotrophic lateral sclerosis, dementia, retinopathy, muscle spasm, migraine, vomiting and dyskinesia. Also useful for the treatment of symptoms associated with Parkinson's diseases and parkinsonism, anxiety, or epilepsy.
ADVANTAGE - (I)-(III) Provide treatment without adverse side effects, which includes drowsiness, dry mouth, constipation, blurred vision, headaches, tachycardia and cardiac arrhythmia.

MC CPI: B06-H; B07-D04C; B07-D11; B14-C01; B14-C03; B14-E05; B14-E10C; B14-F01; B14-F02; B14-J01A1; B14-J01A3; B14-J01A4; B14-J01B3; B14-J01B4; B14-J05; B14-J07; B14-M01; B14-N03; B14-N07D; B14-N16; B14-S01

TECH
ORGANIC CHEMISTRY - Preparation: (I)-(III) Are prepared by reacting a 2-chloro-pyridine of formula (IV) with a substituted piperazine of formula (V) in an aprotic solvent to form a compound of formula (VI). (VI) Is then reacted with an iso(thio)cyanate of formula R5-N=C=X in a solvent to form a compound of formula (Ia).

PHARMACEUTICALS - Preferred Composition: The composition additionally comprises an opioid or non-opioid analgesic and an antiemetic agent. Preferred Method: The treatment method additionally involves administering an antidepressant or an antianxiety agent.

L20 ANSWER 7 OF 21 WPIX COPYRIGHT 2007 THE THOMSON CORP on STN
AN 2003-663366 [62] WPIX
DNC C2003-180168 [62]
TI 6-Fluorobicyclo(3.1.0)hexane derivatives are group II **metabotropic glutamate** receptor antagonist useful as antidepressants
DC B05
IN CHAKI S; CHAKI S T P C L; DEAN R; DEAN R T P C L; HIROTA S; HIROTA S T P C L; NAKAZATO A; NAKAZATO A T P C L; OHTA H; OHTA H T P C L; SAKAGAMI K; SAKAGAMI K T P C L; YASUHARA A; YASUHARA A T P C L; DEAN
PA (CHAK-I) CHAKI S; (DEAN-I) DEAN R; (HIRO-I) HIROTA S; (NAKA-I) NAKAZATO A; (OHTA-I) OHTA H; (SAKA-I) SAKAGAMI K; (TAIS-C) TAISHO PHARM CO LTD; (YASU-I) YASUHARA A
CYC 101
PI WO--2003061698 A1 20030731 (200362)* JA 96[2]
AU--2002359923 A1 20030902 (200422) EN
EP-----1459765 A1 20040922 (200462) EN
KR--2004068348 A 20040730 (200475) KO
BR---200215462 A 20041130 (200506) PT
JP--2003561641 X 20050519 (200534) JA 73
US-20050119345 A1 20050602 (200537) EN
CN-----1610557 A 20050427 (200558) ZH
MX--2004006322 A1 20041101 (200558) ES
ZA---200404795 A 20050831 (200561) EN 131
ZA---200502085 A 20050831 (200561) EN 103
HU---200402649 A2 20051028 (200581) HU
NO---200402530 A 20040922 (200612) NO
IN---200401417 P4 20060210 (200619) EN
NZ------533699 A 20060526 (200637) EN
CN-----1281274 C 20061025 (200716) ZH
ADT WO--2003061698 A1 **2002WO-JP0013693 20021226**; IN---200401417 P4 2002WO-JP0136937 P4200212; AU--2002359923 A1 **2002AU-000359923 20021226**; BR---200215462 A **2002BR-000015462 20021226**; CN-----1610557 A **2002CN-000826388 20021226**; EP-----1459765 A1 **2002EP-000793421 20021226**; NZ------533699 A **2002NZ-000533699 20021226**; EP-----1459765 A1 **2002WO-JP0013693 20021226**; BR---200215462 A **2002WO-JP0013693 20021226**; JP--2003561641 X **2002WO-JP0013693 20021226**; US-20050119345 A1 **2002WO-JP0013693 20021226**; MX--2004006322 A1 **2002WO-JP0013693 20021226**; HU---200402649 A2 **2002WO-JP0013693 20021226**; NZ------533699 A **2002WO-JP0013693 20021226**; JP--2003561641 X **2003JP-000561641 20021226**; HU---200402649 A2 **2004HU-000002649 20021226**; NO---200402530 A 2004NO-000002530 20040616; ZA---200404795 A 2004ZA-000004795 20040617; IN---200401417 P4 2004IN-CHENP1417 20040623; KR--2004068348 A 2004KR-000710069 20040625; MX--2004006322 A1 2004MX-000006322 20040625; ZA---200502085 A **2005ZA-000002085 20021226**; US-20050119345 A1 2005US-000500101 20050204; CN-----1281274 C **2002CN-000826388 20021226**
FDT AU--2002359923 A1 Based on WO--2003061698 A; EP-----1459765 A1 Based on WO--2003061698 A; BR---200215462 A Based on WO--2003061698 A; JP--2003561641 X Based on WO--2003061698 A; MX--2004006322 A1 Based on WO--2003061698 A; HU---200402649 A2 Based on WO--2003061698 A; NZ------533699 A Based on WO--2003061698 A
PRAI **2001JP-000395797 20011227**
IC ICM A61K-031/196; **A61K-045/00**; C07C-229/50
ICS A61K-031/194; A61K-031/1966; A61K-031/225; A61K-031/3811; A61P-025/08; A61P-025/14; A61P-025/16; A61P-025/188; A61P-025/22; A61P-025/24; A61P-025/28; A61P-025/30; A61P-043/000; A61P-009/10; C07C-229/500; C07C-237/04; C07C-237/24; C07C-255/54; C07C-255/544; C07D-333/166; A61K-031/381; A61P-025/00; **A61P-025/18**; A61P-043/00; C07D-333/16

IPCI A61K-0031/196 [I,A]; C07C-0229/00 [I,C]; C07C-0229/54 [I,A]; C07C-0237/00 [I,C]; C07C-0237/48 [I,A]; A61K-0031/185 [I,C]; A61K-0031/381 [I,A]; A61K-0031/381 [I,C]; **A61K-0045/00** [I,A]; **A61K-0045/00** [I,C]; A61P-0025/00 [I,C]; **A61P-0025/18** [I,A]; A61P-0043/00 [I,A]; A61P-0043/00 [I,C]; C07C-0229/50 [I,A]; C07C-0255/00 [I,C]; C07C-0255/54 [I,A]; C07D-0333/00 [I,C]; C07D-0333/16 [I,A]

IPCR A61K-0031/00 [I,A]; A61K-0031/00 [I,C]; A61K-0031/185 [I,C]; A61K-0031/196 [I,A]; A61K-0031/198 [I,A]; A61K-0031/381 [I,A]; A61K-0031/381 [I,C]; A61P-0025/00 [I,C]; **A61P-0025/18** [I,A]; A61P-0043/00 [I,A]; A61P-0043/00 [I,C]; C07C-0229/00 [I,C]; C07C-0229/50 [I,A]; C07D-0333/00 [I,C]; C07D-0333/16 [I,A]

AB WO 2003061698 A1 UPAB: 20060202

NOVELTY - 6-Fluorobicyclo(3.1.0)hexane derivatives (I) and their salts and hydrates are new.

DETAILED DESCRIPTION - 6-Fluorobicyclo(3.1.0)hexane derivatives of formula (I) and their salts and hydrates are new.

R1, R2 = H, 1-10C alkoxy, phenoxy, OAlk (optionally substituted by OAlk or 1 or 2 phenyl), 2-6C hydroxyalkoxy, NQQ or NR6CHR7ACOOR8;

Alk = 1-6C alkyl;

Q = H, Alk, AlkOAlk, 2-6C hydroxyalkyl or AlkCOAlk);

R6, R7 = H, Alk (substituted by OH, COOH, phenyl, hydroxyphenyl, naphthyl, heteroaryl, OAlk, SAlk or CONH2), 2-6C alkyl (substituted by NH2, guanidino or SH), 1-10C alkyl, phenyl, hydroxyphenyl or naphthyl; or

R6+R7 = CH2, CH2CH2 or (CH2)3;

R8 = H or carboxyl protecting group;

A = bond, CH2, CH2CH2 or (CH2)3;

R3 = 1-10C acyl, 1-6C acyl (substituted by OAlk, COOAlk, or COOH) 2-10C hydroxyacyl or COCHR7ANHR9;

R9 = H or amino protecting group;

R4, R5 = H, 1-10C alkyl, 2-10C alkenyl, naphthyl 5 membered heteroaryl containing at least one N or phenyl (optionally substituted by 1-5 halo, 1-10C alkyl, 1-10C alkoxy, CF3, phenyl, COOH, NH2, NO2, CN or phenoxy); or

R4+R5 = ring.

An INDEPENDENT CLAIM is also included for antidepressants comprising a group II **metabotropic glutamate** receptor antagonist.

ACTIVITY - Antidepressant; Tranquilizer, Nootropic; Vasotropic; Neuroprotective; Anticonvulsant; Antiparkinsonian; Cerebroprotective.

MECHANISM OF ACTION - Glutamate-Antagonist.

In assays using CHO cells (1R,2R,3R,5R,6R)-2-amino-3-methoxy-6-fluorobicyclo(3.1.0)hexane-2,6-dicarboxylic acid had an IC50 value for (3H)-MGS00008 binding at glutamate **MGluR2** receptors of less than 100 nM (no specific value is given).

USE - (I) is used as group II **metabotropic glutamate** receptor antagonists for treating and preventing depression. (I) may also be useful for treating and preventing e.g. anxiety, bipolar diseases, Alzheimer's disease, Huntington's chorea, Parkinson's diseases, amyotrophic lateral sclerosis, ischemia, cerebral insufficiency, head trauma or spinal cord disorders.

MC CPI: B06-H; B07-H; B10-A15; B10-A17; B10-B01; B10-B02; B10-B03; B10-B04; B10-C02; B10-C03; B10-C04; B10-D01; B10-D03; B14-F02D; B14-J01A1; B14-J01A3; B14-J01A4; B14-J01B3; B14-J01B4; B14-L06; B14-N16; B14-N17B; B14-S01

TECH

ORGANIC CHEMISTRY - Preparation: (I) are prepared e.g. by acylating a compound corresponding to (I; R3 = H).

L20 ANSWER 8 OF 21 WPIX COPYRIGHT 2007 THE THOMSON CORP on STN

AN 2003-646033 [61] WPIX

CR 2003-449132; 2003-607838; 2003-618015; 2003-636590; 2004-330064

DNC C2003-176749 [61]

TI New heteroaryl substituted pyrroles useful in the treatment or prevention of e.g. pain, depression and bipolar disorder

DC B02; B03

IN COSFORD N D P; HUANG D; SMITH N D

PA (COSF-I) COSFORD N D P; (HUAN-I) HUANG D; (MERI-C) MERCK & CO INC; (SMIT-I) SMITH N D
CYC 100
PI WO--2003059904 A1 20030724 (200361)* EN 67[0]
AU--2002364906 A1 20030730 (200421) EN
EP-----1458710 A1 20040922 (200462) EN
US-20050085514 A1 20050421 (200531) EN
JP--2005516969 W 20050609 (200538) JA 55
ADT WO--2003059904 A1 **2002WO-US0040486 20021217**; US-20050085514 A1 Provisional **2001US-000343262P 20011221**; AU--2002364906 A1 **2002AU-000364906 20021217**; EP-----1458710 A1 **2002EP-000801209 20021217**; EP-----1458710 A1 **2002WO-US0040486 20021217**; US-20050085514 A1 **2002WO-US0040486 20021217**; JP--2005516969 W **2002WO-US0040486 20021217**; JP--2005516969 W **2003JP-000560007 20021217**; US-20050085514 A1 2004US-000499393 20040617
FDT AU--2002364906 A1 Based on WO--2003059904 A; EP-----1458710 A1 Based on WO--2003059904 A; JP--2005516969 W Based on WO--2003059904 A
PRAI **2001US-000343262P 20011221**
2004US-000499393 20040617
IC ICM C07D-401/04
IPCR A61K-0031/427 [I,A]; A61K-0031/427 [I,C]; A61K-0031/4427 [I,C]; A61K-0031/4439 [I,A]; A61K-0031/444 [I,A]; A61P-0001/00 [I,C]; A61P-0001/14 [I,A]; A61P-0021/00 [I,A]; A61P-0021/00 [I,C]; A61P-0025/00 [I,C]; A61P-0025/04 [I,A]; A61P-0025/08 [I,A]; A61P-0025/14 [I,A]; A61P-0025/16 [I,A]; **A61P-0025/18** [I,A]; A61P-0025/20 [I,A]; A61P-0025/22 [I,A]; A61P-0025/24 [I,A]; A61P-0025/28 [I,A]; A61P-0025/30 [I,A]; A61P-0003/00 [I,C]; A61P-0003/04 [I,A]; C07D-0401/00 [I,C]; C07D-0401/04 [I,A]; C07D-0401/14 [I,A]; C07D-0403/00 [I,C]; C07D-0403/04 [I,A]; C07D-0417/00 [I,C]; C07D-0417/04 [I,A]
AB WO 2003059904 A1 UPAB: 20060120
NOVELTY - Heteroaryl substituted pyrroles (I) are new.

DETAILED DESCRIPTION - Heteroaryl substituted pyrroles of formula (I) or their salt are new.

X, Y = (hetero)aryl (optionally mono- - hepta-substituted by Q);

Q = halo, -CN, NO2, 1-6C alkyl (optionally mono- - penta-substituted by T), 1-6C alkenyl, 1-6C alkynyl, -OR1, -NR1R2, -C(=NR1)NR2R3, N(=NR1)NR2R3, -NR1COR2, -NR1CO2R2, -NR1SO2R4, -NR1CONR2R3, -SR4, -SOR4, -SO2R4, -SO2NR1R2, -COR1, -CO2R1, -CONR1R2, -C(=NR1)R2 or C(=NOR1)R2;

T = halo, -CN, -1-6C alkyl, -O-(0-6C alkyl), -O-(3-7C cycloalkyl), -O-(hetero)aryl, -N-(0-6C alkyl)(0-6C alkyl), -N-(0-6C alkyl)(3-7C cycloalkyl) or -N-(0-6C alkyl)(aryl);

R1 - R3 = 0-6C alkyl, 3-7C cycloalkyl or (hetero)aryl (all optionally mono- - penta-substituted by T);

R4 = 1-6C alkyl, 3-7C cycloalkyl or (hetero)aryl (all optionally mono- - penta-substituted by T);

A = 0-4C alkyl, 0-2C-alkyl-SO-(0-2C alkyl), 0-2C-alkyl-SO2-(0-2C alkyl), 0-2C-alkyl-CO-(0-2C alkyl), 0-2C-alkyl-NR9CO-(0-2C alkyl), 0-2C-alkyl-NR9SO2-(0-2C alkyl) or hetero-(0-4C alkyl);

B' = 0-4C alkyl, 0-2C-alkyl-SO-(0-2C alkyl), 0-2C-alkyl-SO2-(0-2C alkyl), 0-2C-alkyl-CO-(0-2C alkyl), 0-2C-alkyl-NR10CO-(0-2C alkyl), 0-2C-alkyl-NR10SO2-(0-2C alkyl) or hetero-(0-4C alkyl);

R9, R10 = 0-6C alkyl, 3-7C cycloalkyl or (hetero)aryl (all optionally mono- - penta-substituted by T); and

R11 - R13 = halo, 0-6C alkyl, 0-6C alkoxyl, O, =N(0-4C alkyl) or -N(0-4C alkyl) (where 1-6C alkyl is optionally mono- - penta-substituted by T).

Two substituents of X and Y are combined to form (hetero)cycloalkyl ring (both optionally mono- - penta-substituted by T) fused to X. Optionally two of R11 - R13 are combined to form (hetero)cycloalkyl (optionally mono- - penta-substituted by T), or (hetero)aryl fused to pyrrole group. Any N is optionally an N-oxide. Any alkyl is optionally mono- - nano-substituted by halo.

ACTIVITY - Analgesic; Antidepressant; Antiaddictive; Nootropic; Neuroprotective; Neuroleptic; Tranquilizer; Antipsychotic;

Antiparkinsonian; Anticonvulsant; Antiaddictive; Anorectic; Anabolic; Antiinflammatory; Hypnotic.

MECHANISM OF ACTION - **Metabotropic glutamate** receptor-5 (**mGluR5**) modulator.

The **mGluR5** inhibitory activity of (I) was examined against **hmGluR5a** receptor expressed in mouse fibroblast Ltk cells (the **hmGluR5a**/L38 cell line) using calcium flux assay. (I) showed IC50 of less than 10 (preferably less than 1 micro M).

USE - For treating or preventing pain (e.g. acute pain, persistent pain, chronic pain, inflammatory pain and neuropathic pain), depression, bipolar disorder, psychosis, drug withdrawal, memory loss, cognitive impairment, dementia, Alzheimer's disease, schizophrenia, panic, disorders of extrapyramidal motor function (e.g. Parkinson's disease, progressive supramuscular palsy, Huntington's disease, Gilles de la Tourette syndrome, and tardive dyskinesia), anxiety disorders (e.g. panic attack, agoraphobia or specific phobias, obsessive-compulsive disorders, post-traumatic stress disorder, acute stress disorder, generalized anxiety disorder, eating disorder, substance-induced anxiety disorder and non-specified anxiety disorder), epilepsy, drug abuse, drug addiction, circadian rhythm, sleep disorder (e.g. shift-work induced sleep disorder and jet-lag) and obesity (all claimed).

ADVANTAGE - The compounds inhibit **mGluR5** with minimal side effects.

MC CPI: B05-A01B; B06-E05; B06-F05; B07-D02; B07-D04C; B07-D11; B07-D12; B10-A09B; B10-A13A; B10-B02E; B10-C04E; B14-C01; B14-E11; B14-E12; B14-J01; B14-J01A1; B14-J01A3; B14-J01A4; B14-J01B1; B14-J01B3; B14-J01B4; B14-J02; B14-L01; B14-L06

TECH

ORGANIC CHEMISTRY - Preparation: Preparation of (I') involves cross-coupling a derivatized pyrrole of formula (i) with moiety of formula (ii) in the presence of catalyst (e.g. Pd(PPh3)4, or Pd on carbon) in a solvent (e.g. tetrahydrofuran or toluene) at 30 - 150 degrees C.
E = metallic of metalloid species.
PHARMACEUTICALS - Preferred Composition: The composition further comprises opiate agonist, opiate antagonist, calcium channel antagonist, 5-hydroxytryptamine (5-HT) receptor agonist, 5HT receptor antagonist, sodium channel antagonist, N-methyl-D-aspartate (NMDA) receptor agonist, NMDA receptor antagonist, cyclooxygenase (COX-2) selective inhibitor, NK1 antagonist, non-steroidal anti-inflammatory drug, gamma-aminobutyric acid (GABA)-A receptor modulator, dopamine agonist, dopamine antagonist, selective serotonin reuptake inhibitor, tricyclic antidepressant drug, norepinephrine modulator, L-dihydroxyphenylalanine (DOPA), buspirone, lithium salt, valproate, neurontin, **olanzapine**, nicotinic agonist, nicotinic antagonist, muscarinic agonist, muscarinic antagonist, a selective serotonin and norepinephrine reuptake inhibitor, heroin substituting drug (e.g. methadone, levo-alpha-acetylmethadol, buprenorphine or naltrexone), disulfiram or acamprosate.

L20 ANSWER 9 OF 21 WPIX COPYRIGHT 2007 THE THOMSON CORP on STN
AN 2003-636590 [60] WPIX
CR 2003-449132; 2003-607838; 2003-618015; 2003-646033; 2004-330064
DNC C2003-173981 [60]
TI New heteroaryl substituted imidazole compounds useful as **metabotropic glutamate** receptor modulator in the treatment of psychiatric and mood disorders e.g. schizophrenia, anxiety, depression and bipolar disorders
DC B03
IN COSFORD N D P; HUANG D; SMITH N D
PA (COSF-I) COSFORD N D P; (HUAN-I) HUANG D; (MERI-C) MERCK & CO INC; (SMIT-I) SMITH N D
CYC 100
PI WO--2003053922 A2 20030703 (200360)* EN 23[0]
AU--2002360621 A1 20030709 (200428) EN
EP-----1458385 A2 20040922 (200462) EN
US-20040259917 A1 20041223 (200504) EN
JP--2005516950 W 20050609 (200538) JA 37

AU--2002360621 B2 20070125 (200731) EN

ADT WO--2003053922 A2 **2002WO-US0040237 20021216**; US-20040259917 A1 Provisional **2001US-000341963P 20011219**; AU--2002360621 A1 **2002AU-000360621 20021216**; EP-----1458385 A2 **2002EP-000795893 20021216**; EP-----1458385 A2 **2002WO-US0040237 20021216**; US-20040259917 A1 **2002WO-US0040237 20021216**; JP--2005516950 W **2002WO-US0040237 20021216**; JP--2005516950 W **2003JP-000554639 20021216**; US-20040259917 A1 2004US-000499392 20040617; AU--2002360621 B2 **2002AU-000360621 20021216**

FDT AU--2002360621 A1 Based on WO--2003053922 A; EP-----1458385 A2 Based on WO--2003053922 A; JP--2005516950 W Based on WO--2003053922 A; AU--2002360621 B2 Based on WO--2003053922 A

PRAI **2001US-000341963P 20011219**
2004US-000499392 20040617

IC ICM C07D-401/04
ICS A61K-031/4439; **A61K-045/00**; A61P-025/00; A61P-025/02; A61P-025/16; **A61P-025/18**; A61P-025/22; A61P-025/24; A61P-025/28; A61P-025/30; A61P-025/34; A61P-029/00; A61P-003/04; C07D-401/14

IPCI A61K-0031/4427 [I,C]; A61K-0031/4439 [I,A]; **A61K-0045/00** [I,A]; **A61K-0045/00** [I,C]; A61P-0025/00 [I,A]; A61P-0025/00 [I,C]; A61P-0025/02 [I,A]; A61P-0025/16 [I,A]; **A61P-0025/18** [I,A]; A61P-0025/22 [I,A]; A61P-0025/24 [I,A]; A61P-0025/28 [I,A]; A61P-0025/30 [I,A]; A61P-0025/34 [I,A]; A61P-0029/00 [I,A]; A61P-0029/00 [I,C]; A61P-0003/00 [I,C]; A61P-0003/04 [I,A]; C07D-0209/00 [I,C]; C07D-0209/30 [I,A]; C07D-0401/00 [I,C]; C07D-0401/04 [I,A]; C07D-0401/14 [I,A]

IPCR A61K-0031/4427 [I,C]; A61K-0031/4439 [I,A]; **A61K-0045/00** [I,A]; **A61K-0045/00** [I,C]; A61P-0025/00 [I,A]; A61P-0025/00 [I,C]; A61P-0025/02 [I,A]; A61P-0025/16 [I,A]; **A61P-0025/18** [I,A]; A61P-0025/22 [I,A]; A61P-0025/24 [I,A]; A61P-0025/28 [I,A]; A61P-0025/30 [I,A]; A61P-0025/34 [I,A]; A61P-0029/00 [I,A]; A61P-0029/00 [I,C]; A61P-0003/00 [I,C]; A61P-0003/04 [I,A]; C07D-0209/00 [I,C]; C07D-0209/30 [I,A]; C07D-0401/00 [I,C]; C07D-0401/04 [I,A]; C07D-0401/14 [I,A]

AB WO 2003053922 A2 UPAB: 20060120

NOVELTY - Heteroaryl substituted imidazole compounds (I) or their salts are new.

DETAILED DESCRIPTION - Heteroaryl substituted imidazole compounds of formula (I) or their salts are new.

X, Y = (hetero)aryl (optionally mono- to hepta-substituted by T;

T = 1-6C alkyl (optionally mono- to penta-substituted by T1), halo, CN, NO2, -NR1R2, -C(=NR1)NR2R3, -N(=NR1)NR2R3, -NR1COR2, -NR1CO2R2, -NR1SO2R4, -NR1CONR2R3, -SO2NR1R2, -CONR1R2, -C(=NR1)R2 or -C(=NOR1)R2), 2-6C alkenyl, 2-6C alkynyl, -OR1, -SR4, -SOR4, -SO2R4, -COR1 or -CO2R1;

X+T+T, Y+T+T = (hetero)cycloalkyl (optionally mono- to penta-substituted by T1)

T1 = -1-6C alkyl , -O(0-6C alkyl), -O(3-7C cycloalkyl), -N(0-6C alkyl)(0-6C alkyl), -N(0-6C alkyl)(3-7C cycloalkyl), -N(0-6C alkyl)(aryl), halo, CN or -O(hetero)aryl);

R1 - R3, R9, R10 = 0-6C alkyl, -3-7C cycloalkyl or (hetero)aryl (all optionally mono- to penta-substituted by T1);

R4 = -1-6C alkyl, -3-7C cycloalkyl or (hetero)aryl (all optionally substituted by T1);

A = -0-2C alkyl-NR9CO-0-2C alkyl or -0-2C alkyl-NR9SO2-0-2C alkyl or T2;

T2 = -0-4C alkyl, -0-2C alkyl-SO-0-2C alkyl, -0-2C alkyl-SO2-0-2C alkyl, -0-2C alkyl-CO-0-2C alkyl or -hetero-0-4C alkyl;

B = -0-2C alkyl-NR10CO-0-2C alkyl, -0-2C alkyl-NR10SO2-0-2C alkyl or T2;

R11, R12 = -0-6C alkyl, =N(0-4C alkyl), -N(0-4C alkyl)(0-4C alkyl), halo, -0-6C alkoxyl or =O; and

provided that:

(1) any alkyl is optionally mono- - penta-substituted by halo

(2) any N is optionally N-oxide; and

(3) at least one of X and Y is a heteroaryl with N adjacent to the position of attachment to A or B respectively.

An INDEPENDENT CLAIM is included for a pharmaceutical composition comprising (I) and a carrier.

ACTIVITY - Analgesic; Tranquilizer; Antidepressant; Nootropic; Antiaddictive; Antismoking; Neuroprotective; Neuroleptic; Antiparkinsonian; Anticonvulsant; Muscular-Gen.; CNS-Gen.; Eating Disorder-Gen; Anorectic.

MECHANISM OF ACTION - **Metabotropic Glutamate** Receptor Subtype 5 (**mGluR5**) Modulator.

(I) were examined against the huGluR5a receptor stably expressed in mouse fibroblast Ltk-cells as described in Daggett et al., Neuropharmacology 34:871 - 886 (1995). (I) showed IC50 of less than 10 microM, (preferably less than 100 nM). No results for specific compounds given.

USE - (I) are used for treating or preventing pain (including acute, persistent, chronic, inflammatory and neuropathic pain), anxiety, depression, bipolar disorder, psychosis, drug withdrawal, tobacco withdrawal, memory loss, cognitive impairment, dementia, Alzheimer's disease, schizophrenia, panic disorders, extrapyramidal motor function (e.g. Parkinson's disease, progressive supramuscular palsy, Huntington's disease, Gilles de la Tourette syndrome and tardive dyskinesia), anxiety disorders (e.g. panic attack, agorphobia and specific phobias, obsessive-compulsive disorders, post-traumatic stress disorder, acute stress disorder, generalized anxiety disorder, eating disorder, substance-induced anxiety disorder and nonspecific anxiety disorder), epilepsy, inflammatory pain, cognitive dysfunction, drug addiction, drug abuse, circadian rhythm, sleep disorder (e.g. shift-work induced sleep disorder and jet lag) and obesity (all claimed).

ADVANTAGE - The compounds are potent **metabotropic glutamate** receptor subtype 5 (**mGluR5**) modulators, and exhibit minimal side effects.

MC CPI: B04-A04; B05-A01B; B06-H; B07-D05; B07-D09; B07-D11; B07-D12; B10-A04; B10-A09B; B10-B02E; B10-B03B; B10-B04B; B10-C04E; B14-C01; B14-C03; B14-D05C; B14-E11; B14-E12; B14-F02B2; B14-J01; B14-J02A2; B14-J02B2; B14-J02C2; B14-J03; B14-J04; B14-J07; B14-L01; B14-L06; B14-M01B; B14-M01C

TECH

PHARMACEUTICALS - Preferred Composition: The composition additionally comprises an opiate agonist, calcium channel antagonist, 5-hydroxytryptamine (5HT) receptor antagonist, sodium channel antagonist, N-methyl D-aspartate (NMDA) receptor antagonist, cyclooxygenase-2 (COX-2) selective inhibitor, neurokinin-1 (NK1) antagonist, non-steroidal anti-inflammatory drug, gamma-amino butyric acid-A (GABA-A) receptor modulator, dopamine agonist, selective serotonin reuptake inhibitor, tricyclic antidepressant drug, norepinephrine modulator, L-dopamine (L-DOPA), buspirone, lithium salt, valproate, neurontin, **olanzapine**, nicotinic agonist/ antagonist, muscarinic agonist/antagonist, selective serotonin and norepinephrine reuptake inhibitor (SSNRI), heroin substituting drug (methadone, levo-alpha-acetylmethadol, buprenorphine or naltrexone), disulfiram or acamprosate.

ORGANIC CHEMISTRY - Preparation: (I; A and B are absent) is prepared by metal-catalyzed-cross-coupling of a substituted imidazole of formula (II) with a metallic or metalloid species of formula (III) in the presence of a homogenous catalyst (e.g. Pd(PPh3)4) and a base (e.g. K2CO3) in solvent (e.g. tetrahydrofuran) at 30 -150 degrees C for 4 - 48 hours.

E = metallic or metalloid species (preferably B(OR)2 or BiLn).

L20 ANSWER 10 OF 21 WPIX COPYRIGHT 2007 THE THOMSON CORP on STN
AN 2003-618015 [58] WPIX
CR 2003-449132; 2003-607838; 2003-636590; 2003-646033; 2004-330064
DNC C2003-168551 [58]
TI New heteroaryl substituted pyrazole useful for treating e.g. psychiatric and mood disorder
DC B02; B03
IN CHEN C; COSFORD N D P; EASTMAN B W; HUANG D; MUNOZ B; PRASIT P; SMITH N D; HU E

PA (CHEN-I) CHEN C; (COSF-I) COSFORD N D P; (EAST-I) EASTMAN B W; (HUAN-I) HUANG D; (MERI-C) MERCK & CO INC; (MUNO-I) MUNOZ B; (PRAS-I) PRASIT P; (SMIT-I) SMITH N D

CYC 100

PI WO--2003051833 A2 20030626 (200358)* EN 66[0]
AU--2002359714 A1 20030630 (200420) EN
EP-----1458383 A2 20040922 (200462) EN
US-20050026963 A1 20050203 (200511) EN
JP--2005516934 W 20050609 (200538) JA 136
AU--2002359714 B2 20061221 (200729) EN

ADT WO--2003051833 A2 **2002WO-US0040147 20021213**; US-20050026963 A1 Provisional **2001US-000341382P 20011218**; AU--2002359714 A1 **2002AU-000359714 20021213**; EP-----1458383 A2 **2002EP-000794267 20021213**; EP-----1458383 A2 **2002WO-US0040147 20021213**; US-20050026963 A1 **2002WO-US0040147 20021213**; JP--2005516934 W **2002WO-US0040147 20021213**; JP--2005516934 W **2003JP-000552720 20021213**; US-20050026963 A1 2004US-000497122 20040526; AU--2002359714 B2 **2002AU-000359714 20021213**

FDT AU--2002359714 A1 Based on WO--2003051833 A; EP-----1458383 A2 Based on WO--2003051833 A; JP--2005516934 W Based on WO--2003051833 A; AU--2002359714 B2 Based on WO--2003051833 A

PRAI **2001US-000341382P 20011218**
2004US-000497122 20040526

IC ICM C07D-231/38
ICS A61K-031/4155; A61K-031/424; A61K-031/427; A61K-031/4439; A61K-031/444; A61K-031/4709; A61K-031/497; A61K-031/498; A61K-031/506; **A61K-045/00**; A61P-017/06; A61P-021/00; A61P-025/04; A61P-025/08; A61P-025/14; A61P-025/16; **A61P-025/18**; A61P-025/20; A61P-025/22; A61P-025/24; A61P-025/28; A61P-025/30; A61P-025/34; A61P-029/00; A61P-003/04; A61P-043/00; C07D-401/04; C07D-401/14; C07D-403/04; C07D-403/14; C07D-413/04; C07D-413/14; C07D-417/04

IPCI A61K-0031/4155 [I,A]; A61K-0031/4155 [I,C]; A61K-0031/424 [I,A]; A61K-0031/424 [I,C]; A61K-0031/427 [I,A]; A61K-0031/427 [I,C]; A61K-0031/4427 [I,C]; A61K-0031/4439 [I,A]; A61K-0031/444 [I,A]; A61K-0031/4709 [I,A]; A61K-0031/4709 [I,C]; A61K-0031/4965 [I,C]; A61K-0031/497 [I,A]; A61K-0031/498 [I,A]; A61K-0031/498 [I,C]; A61K-0031/506 [I,A]; A61K-0031/506 [I,C]; **A61K-0045/00** [I,A]; **A61K-0045/00** [I,C]; A61P-0017/00 [I,C]; A61P-0017/06 [I,A]; A61P-0021/00 [I,A]; A61P-0021/00 [I,C]; A61P-0025/00 [I,C]; A61P-0025/04 [I,A]; A61P-0025/08 [I,A]; A61P-0025/14 [I,A]; A61P-0025/16 [I,A]; **A61P-0025/18** [I,A]; A61P-0025/20 [I,A]; A61P-0025/22 [I,A]; A61P-0025/24 [I,A]; A61P-0025/28 [I,A]; A61P-0025/30 [I,A]; A61P-0025/34 [I,A]; A61P-0029/00 [I,A]; A61P-0029/00 [I,C]; A61P-0003/00 [I,C]; A61P-0003/04 [I,A]; A61P-0043/00 [I,A]; A61P-0043/00 [I,C]; C07D-0231/00 [I,C]; C07D-0231/38 [I,A]; C07D-0401/00 [I,C]; C07D-0401/04 [I,A]; C07D-0401/14 [I,A]; C07D-0403/00 [I,C]; C07D-0403/04 [I,A]; C07D-0403/14 [I,A]; C07D-0413/00 [I,C]; C07D-0413/04 [I,A]; C07D-0413/14 [I,A]; C07D-0417/00 [I,C]; C07D-0417/04 [I,A]

IPCR A61K-0031/4155 [I,A]; A61K-0031/4155 [I,C]; A61K-0031/424 [I,A]; A61K-0031/424 [I,C]; A61K-0031/427 [I,A]; A61K-0031/427 [I,C]; A61K-0031/4427 [I,C]; A61K-0031/4439 [I,A]; A61K-0031/444 [I,A]; A61K-0031/4709 [I,A]; A61K-0031/4709 [I,C]; A61K-0031/4965 [I,C]; A61K-0031/497 [I,A]; A61K-0031/498 [I,A]; A61K-0031/498 [I,C]; A61K-0031/506 [I,A]; A61K-0031/506 [I,C]; **A61K-0045/00** [I,A]; **A61K-0045/00** [I,C]; A61P-0017/00 [I,C]; A61P-0017/06 [I,A]; A61P-0021/00 [I,A]; A61P-0021/00 [I,C]; A61P-0025/00 [I,C]; A61P-0025/04 [I,A]; A61P-0025/08 [I,A]; A61P-0025/14 [I,A]; A61P-0025/16 [I,A]; **A61P-0025/18** [I,A]; A61P-0025/20 [I,A]; A61P-0025/22 [I,A]; A61P-0025/24 [I,A]; A61P-0025/28 [I,A]; A61P-0025/30 [I,A]; A61P-0025/34 [I,A]; A61P-0029/00 [I,A]; A61P-0029/00 [I,C]; A61P-0003/00 [I,C]; A61P-0003/04 [I,A]; A61P-0043/00 [I,A]; A61P-0043/00 [I,C]; C07D-0231/00 [I,C]; C07D-0231/38 [I,A]; C07D-0401/00 [I,C]; C07D-0401/04 [I,A]; C07D-0401/14 [I,A]; C07D-0403/00 [I,C]; C07D-0403/04 [I,A]; C07D-0403/14 [I,A]; C07D-0413/00 [I,C]; C07D-0413/04 [I,A]; C07D-0413/14 [I,A];

C07D-0417/00 [I,C]; C07D-0417/04 [I,A]

AB WO 2003051833 A2 UPAB: 20060120

NOVELTY - Heteroaryl substituted pyrazole (I) or its salt is new.

DETAILED DESCRIPTION - Heteroaryl substituted pyrazole of formula (I), or its salt is new.

X, Y = (hetero)aryl (optionally mono - hepta substituted by Q);

Q = halo, -CN, NO2, 1-6C alkyl (optionally mono to penta-substituted by T), 1-6C alkenyl, 1-6C alkynyl, -OR1, -NR1R2, -C(=NR1)NR2R3, N(=NR1)NR2R3, -NR1COR2, -NR1CO2R2, -NR1SO2R4, -NR1CONR2R3, -SR4, -SOR4, -SO2R4, -SO2NR1R2, -COR1, -CO2R1, -CONR1R2, -C(=NR1)R2 or C(=NOR1)R2;

T = halo, -CN, -1-6C alkyl, -O-(0-6C alkyl), -O-(3-7C cycloalkyl), -O-((hetero)aryl), -N-(0-6C alkyl)(0-6C alkyl), -N-(0-6C alkyl)(3-7C cycloalkyl) or -N-(0-6C alkyl)(aryl);

R1 - R3 = 0-6C alkyl, 3-7C cycloalkyl or (hetero)aryl (optionally mono to penta-substituted by T);

R4 = 1-6C alkyl, 3-7C cycloalkyl or (hetero)aryl (optionally mono to penta-substituted by T);

A = 0-4C alkyl, 0-2C-alkyl-SO-(0-2C)-alkyl, 0-2C-alkyl-SO2-(0-2C)-alkyl, 0-2C-alkyl-CO-(0-2C)-alkyl, 0-2C-alkyl-NR9CO-(0-2C)-alkyl, 0-2C-alkyl-NR9SO2-(0-2C)-alkyl or hetero-(0-4C)-alkyl;

B' = 0-4C alkyl, 0-2C-alkyl-SO-(0-2C)-alkyl, 0-2C-alkyl-SO2-(0-2C)alkyl, 0-2C-alkyl-CO-(0-2C)alkyl, 0-2C-alkyl-NR10CO-(0-2C)alkyl, 0-2C-alkyl-NR10SO2-(0-2C)alkyl or hetero-(0-4C)alkyl;

R9, R10 = 0-6C alkyl, 3-7C cycloalkyl or (hetero)aryl (optionally mono- to penta-substituted by T);

A1, A2 = N or CR12;

R11, R12 = halo, 0-6C alkyl, 0-6C alkoxyl or -N(0-4C alkyl)(0-4C alkyl) (1-6C alkyl is optionally mono to penta-substituted by T); and

R11+R12 = (hetero)cycloalkyl (optionally mono to penta-substituted by T) or (hetero)aryl ring fused to the pyrazole group.

Two substituents of X and Y are combined to form a cycloalkyl or heterocycloalkyl ring (both optionally mono to penta-substituted by T) fused to X. At least one of X and Y is a heteroaryl with N adjacent to the position of attachment to A or B' respectively. R11 and R12 form =O, =N(0-4C alkyl) using a bond from the adjoining double bond. Any N may be an N-oxide. One of A1 and A2 is N, then the other is CR12. Any alkyl is optionally mono to nano-substituted by halo.

Provided that when X is 2-pyridyl, A1 is N, A2 is CH, R11 and R12 are H, and A and B' are absent, then Y is other than 4-methoxyphenyl or 2,5-dimethoxyphenyl.

An INDEPENDENT CLAIM is also included for a composition comprising (I) optionally in combination with another therapeutic agent.

ACTIVITY - Analgesic; Tranquilizer; Antidepressant; Nootropic; Neuroleptic; Antiaddictive; Antismoking; Anabolic; Antiinflammatory; Neuroprotective; Antiparkinsonian; Muscular; Anticonvulsant; Anorectic; Hypnotic.

MECHANISM OF ACTION - **Metabotropic glutamate** receptor-subtype 5 (**mGluR5**) inhibitor/modulator.

(I) was tested for **mGluR5** inhibitory activity and showed an IC50 value of less than 10 microM. But no specific results are given.

USE - For the treatment or prevention of pain disorder (e.g. acute pain, persistent pain, chronic pain, inflammatory pain and neuropathic pain), anxiety, depression, bipolar disorder, psychosis, drug withdrawal, tobacco withdrawal, memory loss, cognitive impairment, dementia, Alzheimer's disease, schizophrenia and panic), extrapyramidal motor function disorders (e.g. Parkinson's disease, progressive supramuscular palsy, Huntington's disease, Gilles de la Tourette syndrome and tardive dyskinesia), anxiety disorders (e.g. panic attack, agoraphobia or specific phobias, obsessive-compulsive disorders, post traumatic stress disorder, acute stress disorder, generalized anxiety disorder, eating disorder, substance-induced anxiety disorder and non-specified anxiety disorder), neuropathic pain, Parkinson's Disease, depression, epilepsy, inflammatory pain, cognitive dysfunction, drug addiction, drug abuse and drug withdrawal, bipolar disorders, circadian rhythm, sleep disorders (e.g. shift-work induced sleep disorder and jet-lag) and obesity (all claimed).

ADVANTAGE - The compounds inhibit **mGluR5** with fewer side effects.

MC CPI: B06-H; B07-D08; B10-A04; B10-A09B; B10-B02B; B10-B02E; B10-B04B; B10-C04E; B14-C01; B14-C03; B14-E12; B14-J01; B14-J05; B14-J07; B14-L06; B14-M01B; B14-M01C

TECH ORGANIC CHEMISTRY - Preparation: Preparation of (I) (where A and B' are absent, A2 is CR12 and A1 is N) involves
(1) reacting hydrazine group of formula (i) with 1,3-dicarbonyl in a solvent at 30 - 150 degreesC for 1 - 18 hour to form a substituted pyrazole of formula (ii);
(2) derivatizing (ii) to give derivatized pyrazole of formula (iii); and
(3) coupling (iii) with hetero(aryl) derivative of formula (iv).
A' = group capable of undergoing a metal-catalyzed cross-coupling reaction; and
E = metallic or metalloid species.
PHARMACEUTICALS - Preferred Composition: The composition further comprises an opiate agonist, an opiate antagonist, a calcium channel antagonist, a 5HT receptor agonist, a 5HT receptor antagonist, a sodium channel antagonist, an NMDA receptor agonist, an NMDA receptor antagonist, a COX-2 selective inhibitor, an NK1 antagonist, a non-steroidal anti-inflammatory drug, a GABA-A receptor modulator, a dopamine agonist, a dopamine antagonist, a selective serotonin reuptake inhibitor, a tricyclic antidepressant drug, a norepinephrine modulator, L-DOPA, buspirone, a lithium salt, valproate, neurontin, **olanzapine**, a nicotinic agonist, a nicotinic antagonist, a muscarinic agonist, a muscarinic antagonist, a selective serotonin and norepinephrine reuptake inhibitor (SSNRI), a heroin substituting drug, disulfiram or acamprosate.
Preferred Drug: The heroin substituting drug is methadone, levo-alpha-acetylmethadol, buprenorphine or naltrexone.

L20 ANSWER 11 OF 21 WPIX COPYRIGHT 2007 THE THOMSON CORP on STN
AN 2003-607838 [57] WPIX
CR 2003-449132; 2003-618015; 2003-636590; 2003-646033; 2004-330064
DNC C2003-165566 [57]
TI New heteroaryl substituted triazole derivatives useful for the treatment of psychiatric and mood disorders e.g. schizophrenia, anxiety, depression, panic and bipolar disorder
DC B02; B03
IN COSFORD N D P; PRASIT P; ROPPE J R; SMITH N D; TEHRANI L R
PA (COSF-I) COSFORD N D P; (MERI-C) MERCK & CO INC; (PRAS-I) PRASIT P; (ROPP-I) ROPPE J R; (SMIT-I) SMITH N D; (TEHR-I) TEHRANI L R
CYC 100
PI WO--2003051315 A2 20030626 (200357)* EN 28[0]
AU--2002366388 A1 20030630 (200420) EN
EP-----1458708 A2 20040922 (200462) EN
US-20050020585 A1 20050127 (200509) EN
JP--2005516920 W 20050609 (200538) JA 48
US-----7105548 B2 20060912 (200660) EN
ADT WO--2003051315 A2 **2002WO-US0041720 20021213**; US-20050020585 A1 Provisional **2001US-000341582P 20011218**; AU--2002366388 A1 **2002AU-000366388 20021213**; EP-----1458708 A2 **2002EP-000805227 20021213**; EP-----1458708 A2 **2002WO-US0041720 20021213**; US-20050020585 A1 **2002WO-US0041720 20021213**; JP--2005516920 W **2002WO-US0041720 20021213**; JP--2005516920 W **2003JP-000552248 20021213**; US-20050020585 A1 2004US-000499391 20040617; US-----7105548 B2 Provisional **2001US-000341582P 20011218**; US-----7105548 B2 **2002WO-US0041720 20021213**; US-----7105548 B2 2004US-000499391 20040617
FDT AU--2002366388 A1 Based on WO--2003051315 A; EP-----1458708 A2 Based on WO--2003051315 A; JP--2005516920 W Based on WO--2003051315 A; US-----7105548 B2 Based on WO--2003051315 A
PRAI **2001US-000341582P 20011218**
2004US-000499391 20040617
IC ICM C07D-401/04

IPCI A61K-0031/41 [I,A]; A61K-0031/41 [I,C]; A61K-0031/44 [I,A]; A61K-0031/44 [I,C]; C07D-0249/00 [I,C]; C07D-0249/04 [I,A]; C07D-0401/00 [I,A]; C07D-0401/00 [I,C]

IPCR A61K-0031/135 [I,A]; A61K-0031/135 [I,C]; A61K-0031/145 [I,A]; A61K-0031/145 [I,C]; A61K-0031/185 [I,A]; A61K-0031/185 [I,C]; A61K-0031/19 [I,A]; A61K-0031/195 [I,A]; A61K-0031/4427 [I,C]; A61K-0031/4439 [I,A]; A61K-0031/485 [I,A]; A61K-0031/485 [I,C]; A61K-0031/506 [I,A]; A61K-0031/506 [I,C]; A61K-0031/551 [I,C]; A61K-0031/5513 [I,A]; **A61K-0045/00** [I,A]; **A61K-0045/00** [I,C]; **A61K-0045/06** [I,A]; A61P-0021/00 [I,A]; A61P-0021/00 [I,C]; A61P-0025/00 [I,A]; A61P-0025/00 [I,C]; A61P-0025/04 [I,A]; A61P-0025/08 [I,A]; A61P-0025/14 [I,A]; A61P-0025/16 [I,A]; **A61P-0025/18** [I,A]; A61P-0025/20 [I,A]; A61P-0025/22 [I,A]; A61P-0025/24 [I,A]; A61P-0025/28 [I,A]; A61P-0025/30 [I,A]; A61P-0029/00 [I,A]; A61P-0029/00 [I,C]; A61P-0003/00 [I,C]; A61P-0003/04 [I,A]; A61P-0003/12 [I,A]; A61P-0003/14 [I,A]; C07D-0401/00 [I,C]; C07D-0401/04 [I,A]; C07D-0401/14 [I,A]

AB WO 2003051315 A2 UPAB: 20060120

NOVELTY - Heteroaryl substituted triazole derivatives (I) are new.

DETAILED DESCRIPTION - Heteroaryl substituted triazole derivatives of formula (I) or their salts are new.

X = (hetero)aryl (optionally substituted by 1-7 of Q);

Q = halo, -CN, NO2, 1-6C alkyl (optionally substituted by 1-5 of T'), 2-6C alkenyl, 2-6C alkynyl, -OR1, -NR1R2, -C(=NR1)NR2R3, N(=NR1)NR2R3, -NR1COR2, -NR1CO2R2, -NR1SO2R4, -NR1CONR2R3, -SR4, -SOR4, -SO2R4, -SO2NR1R2, -COR1, -CO2R1, -CONR1R2, -C(=NR1)R2, or C(=NOR1)R2;

T' = halo, -CN, 1-6C alkyl, -O-(0-6C alkyl), -O-(3-7C cycloalkyl), -O-((hetero)aryl), -N-(0-6C alkyl)(0-6C alkyl), -N-(0-6C alkyl)(3-7C cycloalkyl), or -N-(0-6C alkyl)(aryl);

A1 - A5 = N or C;

R1 - R3, R5 - R7, R9 and R10 = 0-6C alkyl, 3-7C cycloalkyl or (hetero)aryl (all optionally substituted by 1-5 T');

R4 and R8 = 1-6C alkyl, 3-7C cycloalkyl, or (hetero)aryl (all optionally substituted by 1-5 of T');

A = 0-4C alkyl, 0-2C alkyl-SO-(0-2C alkyl)-, 0-2C alkyl-SO2-(0-2C alkyl), 0-2C alkyl-CO-(0-2C alkyl)-, 0-2C alkyl-NR9CO-(0-2C alkyl), 0-2C alkyl-NR9SO2-(0-2C alkyl) or -hetero-(0-4C alkyl);

Y' = (hetero)aryl (optionally substituted by 1-7 of Q1);

Q1 = halo, -CN, NO2, -1-6C alkyl (optionally substituted by 1-5 of T'), -2-6C alkenyl, -2-6C alkynyl, -OR5, -NR5R6, -C(=NR5)NR6R7, N(=NR5)NR6R7, -NR5COR6, -NR5CO2R6, -NR5SO2R8, -NR5CONR6R7, -SR8, -SOR8, -SO2R8, -SO2NR5R6, -COR5, -CO2R5, -CONR5R6, -C(=NR5)R6, or C(=NOR5)R6;

B' = 0-4C alkyl, 0-2C alkyl-SO-(0-2C alkyl)-, -0-2C alkyl-SO2-(0-2C alkyl)-, -0-2C alkyl-CO-(0-2C alkyl), -0-2C alkyl-NR10CO-(0-2C alkyl)-, -0-2C alkyl-NR10SO2-(0-2C alkyl), or -hetero-(0-4C alkyl); and

R11 = halo, -0-6C alkyl, -0-6C alkoxyl, =O, =N(0-4C alkyl), or N(0-4C alkyl)(0-4C alkyl).

Optionally two substituents of X and Y' are combined to form a (hetero)cycloalkyl ring (both optionally substituted by 1-5 T) fused to X and Y' respectively. At least one of X and Y is (hetero)aryl with N adjacent to the position of attachment to A or B respectively. Provided that:

(1) three of A1 - A5 are N and the remaining are C;

(2) one of A1 and A4 must be N but both A1 and A4 are N; and

(3) when X is 2-pyridyl, A1 and A3 are C, A2, A4 and A5 are N, A and B are direct bond and R11 is OH, then Y' is not unsubstituted phenyl or 4-methoxyphenyl.

ACTIVITY - Analgesic; Antiinflammatory; Tranquilizer; Antidepressant; Nootropic; Neuroleptic; Antismoking; Neuroprotective; Antiparkinsonian; Anticonvulsant; Muscular; Antiaddictive; Anorectic.

MECHANISM OF ACTION - **Metabotropic glutamate** receptor-subtype 5 (**mGluR5**) modulator/inhibitor.

The inhibitory activity of 2-(1-(3-chlorophenyl)-1H-1,2,4-triazol-3-yl)pyridine (A) against **hmGluR5a** receptor stably expressed in mouse fibroblast Ltk-cells was tested in terms of intracellular calcium ((Ca2+)i). The **hmGluR5a**/L38-20 cells were plated onto 96-well

plates and loaded with fura-2 (3 microM) for 1 hour. The cell plate was transferred to a 96-channel fluorimeter which was integrated into a fully automated plate handling and liquid delivery system. The glutamate (10 microM) was added to the well and the glutamate-evoked increase in (Ca')i in the presence of the screening compound was measured. (A) showed an IC50 value of 10 microM.

USE - For treatment or prevention of a pain disorder (e.g. acute pain, persistent pain, chronic pain, inflammatory pain and neuropathic pain), anxiety, depression, bipolar disorder, psychosis, drug withdrawal, tobacco withdrawal, memory loss, cognitive impairment, dementia, Alzheimer's disease, schizophrenia, extrapyramidal motor function disorder (e.g. Parkinson's disease, progressive supramuscular palsy, Huntington's disease, Gilles de la Tourette syndrome and tardive dyskinesia), anxiety disorder (e.g. panic attack, agoraphobia or specific phobias, obsessive-compulsive disorders, post-traumatic stress disorder, acute stress disorder, generalized anxiety disorder, eating disorder, substance-induced anxiety disorder and non-specified anxiety disorder), epilepsy, drug addiction, drug abuse, circadian rhythm, sleep disorder (e.g. shift-work induced sleep disorder and jet-lag) and obesity (all claimed).

ADVANTAGE - The compounds inhibit **metabotropic glutamate** receptor-subtype 5 (**mGluR5**) with fewer side effects.

MC CPI: B04-A04; B05-A01B; B06-H; B07-D04C; B07-D13; B07-H; B10-A04; B10-A09B; B10-B02E; B10-B02G; B10-B04B; B10-C04E; B14-C01; B14-C03; B14-D05C; B14-D06; B14-E11; B14-E12; B14-F02B2; B14-J01; B14-J01A; B14-J01B; B14-J02; B14-J03; B14-J04; B14-J05A; B14-J05D; B14-J07; B14-L01; B14-L06; B14-M01B; B14-M01C

TECH

ORGANIC CHEMISTRY - Preparation: Preparation of (I) (where A and B' are absent, A2, A5 and A4 are N, and A1 and A3 are C) involves:
(1) reacting a nitrile derivative of formula (i) with hydrazine hydrate in a solvent at 0 - 100 degrees C to give a substituted amidrazone derivative of formula (ii);
(2) cyclizing (ii) under hot HCO2H or trialkylorthoformate to give monosubstituted 1,2,4-triazole derivative of formula (iii); and
(3) coupling (iii) with hetero(aryl) derivative of formula (iv).
W' = metalloid species, halo or group capable of undergoing a metal catalyzed N-arylation cross-coupling reaction.
PHARMACEUTICALS - Preferred Components: The composition additionally comprises opiate agonist/antagonist, calcium channel antagonist, 5HT receptor agonist/antagonist, sodium channel antagonist, an NMDA receptor agonist/antagonist, COX-2 selective inhibitor, NK1 antagonist, non-steroidal anti-inflammatory drug, GABA-A receptor modulator, dopamine agonist/antagonist, selective serotonin reuptake inhibitor, tricyclic antidepressant drug, norepinephrine modulator, L-DOPA, buspirone, lithium salt, valproate, neurontin, **olanzapine**, nicotinic agonist, nicotinic antagonist, muscarinic agonist/antagonist, selective serotonin and norepinephrine reuptake inhibitor (SSNRI), heroin substituting drug (preferably methadone, levo-alpha-acetylmethadol, buprenorphine or naltrexone), disulfiram, or acamprosate.

L20 ANSWER 12 OF 21 WPIX COPYRIGHT 2007 THE THOMSON CORP on STN
AN 2003-541545 [51] WPIX
DNC C2003-146953 [51]
TI New fused heterobicyclo substituted phenyl compounds useful for treating or preventing e.g. pain, anxiety, depression, bipolar disorder, psychosis, or drug withdrawal
DC B02
IN ARRUDA J; BONNEFOUS C; CAMPBELL B T; CUBE R V; MUNOZ B; STEARNS B; VERNIER J; VERNIER J M; WANG B; ZHAO X
PA (ARRU-I) ARRUDA J; (BONN-I) BONNEFOUS C; (CAMP-I) CAMPBELL B T; (CUBE-I) CUBE R V; (MERI-C) MERCK & CO INC; (MUNO-I) MUNOZ B; (STEA-I) STEARNS B; (VERN-I) VERNIER J; (WANG-I) WANG B; (ZHAO-I) ZHAO X
CYC 100
PI WO--2003048137 A1 20030612 (200351)* EN 57[0]

AU--2002365892 A1 20030617 (200419) EN
EP-----1453815 A1 20040908 (200459) EN
US-20050065340 A1 20050324 (200526) EN
JP--2005514382 W 20050519 (200538) JA 98
US-----7087601 B2 20060808 (200652) EN

ADT WO--2003048137 A1 **2002WO-US0038201 20021126**; US-20050065340 A1 Provisional **2001US-000334547P 20011130**; AU--2002365892 A1 **2002AU-000365892 20021126**; EP-----1453815 A1 **2002EP-000804470 20021126**; EP-----1453815 A1 **2002WO-US0038201 20021126**; US-20050065340 A1 **2002WO-US0038201 20021126**; JP--2005514382 W **2002WO-US0038201 20021126**; JP--2005514382 W **2003JP-000549329 20021126**; US-20050065340 A1 2004US-000497452 20041109; US-----7087601 B2 Provisional **2001US-000334547P 20011130**; US-----7087601 B2 **2002WO-US0038201 20021126**; US-----7087601 B2 2004US-000497452 20041109

FDT AU--2002365892 A1 Based on WO--2003048137 A; EP-----1453815 A1 Based on WO--2003048137 A; JP--2005514382 W Based on WO--2003048137 A; US-----7087601 B2 Based on WO--2003048137 A

PRAI **2001US-000334547P 20011130**
2004US-000497452 20041109

IC ICM C07D-263/56

IPCI A61K-0031/4353 [I,C]; A61K-0031/437 [I,A]; A61K-0031/5375 [I,C]; A61K-0031/5383 [I,A]; C07D-0413/00 [I,C]; C07D-0413/14 [I,A]; C07D-0491/00 [I,C]; C07D-0491/048 [I,A]

IPCR A61K-0031/422 [I,A]; A61K-0031/422 [I,C]; A61K-0031/423 [I,A]; A61K-0031/423 [I,C]; A61K-0031/4353 [I,C]; A61K-0031/437 [I,A]; A61K-0031/4427 [I,C]; A61K-0031/4439 [I,A]; A61K-0031/4523 [I,C]; A61K-0031/454 [I,A]; A61K-0031/506 [I,A]; A61K-0031/506 [I,C]; A61K-0031/5375 [I,C]; A61K-0031/5377 [I,A]; **A61K-0045/00** [I,A]; **A61K-0045/00** [I,C]; A61P-0025/00 [I,A]; A61P-0025/00 [I,C]; A61P-0025/04 [I,A]; A61P-0025/08 [I,A]; A61P-0025/14 [I,A]; A61P-0025/16 [I,A]; **A61P-0025/18** [I,A]; A61P-0025/22 [I,A]; A61P-0025/24 [I,A]; A61P-0025/28 [I,A]; A61P-0025/30 [I,A]; A61P-0025/34 [I,A]; A61P-0025/36 [I,A]; A61P-0029/00 [I,A]; A61P-0029/00 [I,C]; A61P-0043/00 [I,A]; A61P-0043/00 [I,C]; C07D-0263/00 [I,C]; C07D-0263/56 [I,A]; C07D-0263/57 [I,A]; C07D-0413/00 [I,C]; C07D-0413/10 [I,A]; C07D-0498/00 [I,C]; C07D-0498/04 [I,A]; C07D-0521/00 [I,A]; C07D-0521/00 [I,C]

AB WO 2003048137 A1 UPAB: 20060119

NOVELTY - Fused heterobicyclo substituted phenyl compounds (I) are new.

DETAILED DESCRIPTION - Fused heterobicyclo substituted phenyl compounds of formula (I) and their salts are new.

dotted line = optional double bond;

X = N, CH or NH;

Y = O or N-R4;

Z1-Z4 = N, NH, CH or CH2;

R1 = 1-6C alkyl, 1-4C alkoxyl, 3-6C cycloalkyl, 0-4C alkyl-phenyl, 0-4C alkyl-pyridyl, 0-4C alkyl-imidazolyl, 0-4C alkyl-pyrazolyl, 0-4C alkyl-triazolyl, 0-4C alkyl-tetrazolyl, 0-4C alkyl-dioxolanyl, 0-4C alkyl-thiazolyl, 0-4C alkyl-piperidinyl, 0-4C alkyl-pyrrolidinyl, 0-4C alkyl-morpholinyl, 0-4C alkyl-pyrimidinyl, 2-6C alkynyl-thiazolyl or N(0-4C alkyl)2 (all optionally substituted by 1-5 T), OH, halo or CN;

T = halo, OH, CN, 1-6C alkyl, 1-4C alkoxyl, N(0-4C alkyl)2, 0-4C alkyl-COO-0-4C alkyl, 0-4C alkyl-morpholinyl or 0-4C alkyl-benzoxazolyl;

R2 = H, halo, OH, CN, N(0-4C alkyl)2, NO2, 1-6C alkyl, 1-4C alkoxyl, 0-4C alkyl-phenyl or 1-4C alkoxy-phenyl (all optionally substituted by 1-3 halo, OH, CN or 1-4C alkoxy);

R3 = H or -1-4C alkoxyl;

R4 = 0-4C alkyl; and

R5 = H, halo or 1-4C alkyl;

provided that:

(i) one of Z1-Z4 is optionally N or NH; and

(ii) when X = N and Y = O, then Z1-Z4 = CH, R1 = 1-6C alkyl, 3-6C cycloalkyl, 0-4C alkyl-triazolyl, 0-4C alkyl-imidazolyl, 0-4C alkyl-pyrazolyl, 0-4C alkyl-tetrazolyl, 0-4C alkyl-pyrrolidinyl, 0-4C alkyl-piperidinyl, 0-4C alkyl-pyridyl, 0-4C alkyl-pyrimidinyl or 0-4C

alkyl-morpholinyl (all optionally substituted by 1-5 T), and R2 = 0-4C alkyl-phenyl, 1-6C alkyl, NO2, N(0-4C alkyl)2, 1-6C alkoxy-phenyl or 1-6C alkoxyl (all optionally substituted by halo, OH, CN or 1-4C alkoxy).

ACTIVITY - Analgesic; Tranquilizer; Antidepressant; Nootropic; Neuroleptic; Antiaddictive; Antismoking; Neuroprotective; Antiparkinsonian; Eating-Disorders-Gen.; Anticonvulsant.

MECHANISM OF ACTION - **Metabotropic Glutamate** Receptor-5 Modulator. Compounds (I) were tested for **mgluR5** inhibitory activity using calcium flux assay in terms of intracellular calcium (see Daggett et al., Neuropharmacology, 34:871-886 (1995)). Compounds (I) exhibited **mGluR5** inhibitory activity of less than 5 microM (preferred compounds (I) less than 50 nM). No specific data given.

USE - For treating or preventing pain (e.g. acute pain, persistent pain, chronic pain, inflammatory pain and neuropathic pain), anxiety, depression, bipolar disorder, psychosis, drug withdrawal, tobacco withdrawal, memory loss, cognitive impairment, dementia, Alzheimer's disease, schizophrenia, panic, disorder of extrapyramidal motor function (e.g. Parkinson's disease, progressive supramuscular palsy, Huntington's disease, Gilles de la Tourette syndrome or tardive dyskinesia), anxiety disorder (e.g. panic attack, agoraphobia or specific phobias, obsessive-compulsive disorders, post-traumatic stress disorder, acute stress disorder, generalized anxiety disorder, eating disorders, substance-induced anxiety disorder or nonspecified anxiety disorder), neuropathic pain, epilepsy, inflammatory pain, cognitive dysfunction, drug addition (claimed) and drug abuse.

ADVANTAGE - (I) Displays minimal side effects.

MC CPI: B06-E01; B14-C01; B14-C03; B14-J01A1; B14-J01A3; B14-J01A4; B14-J01B3; B14-J01B4; B14-J02B2; B14-J02D3; B14-J04; B14-J07; B14-M01B; B14-M01C

TECH

ORGANIC CHEMISTRY - Preparation: (I) Are prepared e.g. by reacting a benzoic acid chloride of formula (II) with 2-aminophenol to give a heterobicyclic compound of formula (III) to give (I; R2 = Me; Z1-Z4 = CH; X = N; Y = O; R5 = H).

PHARMACEUTICALS - Preferred Composition: The composition additionally comprises an opiate agonist, opiate antagonist, calcium channel antagonist, 5-hydroxytryptamine (5HT) receptor agonist, 5HT receptor antagonist, sodium channel antagonist, N-methyl-D-aspartate (NMDA) receptor agonist, NMDA receptor antagonist, cyclooxygenase (COX)-2 selective inhibitor, neurokinin (NK)1 antagonist, non-steroidal anti-inflammatory drug, gamma-aminobutyric acid (GABA)-A receptor modulator, dopamine agonist, dopamine antagonist, selective serotonin reuptake inhibitor, tricyclic antidepressant drug, norepinephrine modulator, L-dihydroxyphenylalanine (L-DOPA), buspirone, lithium salt, valproate, neurontin, **olanzapine**, nicotinic agonist, nicotinic antagonist, muscarinic agonist, muscarinic antagonist, selective serotonin and norepinephrine reuptake inhibitor (SSNRI), heroin substituting drug, disulfiram or acamprosate.

Preferred Components: The heroin substituted drug is methadone, levo-alpha-acetylmethadol, buprenorphine or naltrexone.

L20 ANSWER 13 OF 21 WPIX COPYRIGHT 2007 THE THOMSON CORP on STN
AN 2003-513697 [48] WPIX
DNC C2003-137605 [48]
TI New acetylene derivatives useful for treating nervous system disorders mediated by human **metabotropic glutamate** receptor e.g. Parkinson's disease and Alzheimer's disease
DC B05
IN AUBERSON Y; GASPARINI F; OFNER S; SILVIO O; HART T W; ZIMMERMANN K
PA (AUBE-I) AUBERSON Y; (GASP-I) GASPARINI F; (NOVS-C) NOVARTIS AG; (NOVS-C) NOVARTIS PHARMA GMBH; (OFNE-I) OFNER S
CYC 89
PI WO--2003047581 A1 20030612 (200348)* EN 17[0]
AU--2002358585 A1 20030617 (200419) EN
EP-----1453512 A1 20040908 (200459) EN

BR---200214666 A 20041103 (200482) PT
NO---200402673 A 20040625 (200513) NO
NZ------533266 A 20050225 (200519) EN
HU---200402191 A2 20050228 (200523) HU
US-20050065191 A1 20050324 (200526) EN
JP--2005514381 W 20050519 (200538) JA 26
CN-----1592623 A 20050309 (200542) ZH
TW---200304910 A 20031016 (200557) ZH
MX--2004005456 A1 20041101 (200558) ES
ZA---200403713 A 20051026 (200577) EN 37
IN---200401200 P4 20060210 (200619) EN
EP-----1453512 B1 20060531 (200637) EN
KR--2005044657 A 20050512 (200637) KO
DE----60211944 E 20060706 (200648) DE
EP-----1453512 B8 20060719 (200648) EN
AU--2002358585 B2 20060119 (200655) EN
ES-----2263842 T3 20061216 (200710) ES
DE----60211944 T2 20070516 (200734) DE

ADT WO--2003047581 A1 **2002WO-EP0013670 20021203**; IN---200401200 P4 2002WO-EP0136700 P4200212; TW---200304910 A **2002TW-000134933 20021202**; AU--2002358585 A1 **2002AU-000358585 20021203**; AU--2002358585 B2 **2002AU-000358585 20021203**; BR---200214666 A **2002BR-000014666 20021203**; CN-----1592623 A **2002CN-000823296 20021203**; DE----60211944 E **2002DE-000611944 20021203**; EP-----1453512 A1 **2002EP-000792867 20021203**; EP-----1453512 B1 **2002EP-000792867 20021203**; EP-----1453512 B8 **2002EP-000792867 20021203**; DE----60211944 E **2002EP-000792867 20021203**; ES-----2263842 T3 **2002EP-000792867 20021203**; NZ------533266 A **2002NZ-000533266 20021203**; EP-----1453512 A1 **2002WO-EP0013670 20021203**; BR---200214666 A **2002WO-EP0001367 20021203**; NO---200402673 A **2002WO-EP0013670 20021203**; NZ------533266 A **2002WO-EP0013670 20021203**; HU---200402191 A2 **2002WO-EP0013670 20021203**; US-20050065191 A1 **2002WO-EP0013670 20021203**; JP--2005514381 W **2002WO-EP0013670 20021203**; MX--2004005456 A1 **2002WO-EP0013670 20021203**; EP-----1453512 B1 **2002WO-EP0013670 20021203**; KR--2005044657 A **2002WO-EP0013670 20021203**; EP-----1453512 B8 **2002WO-EP0013670 20021203**; DE----60211944 E **2002WO-EP0013670 20021203**; JP--2005514381 W **2003JP-000548836 20021203**; HU---200402191 A2 **2004HU-000002191 20021203**; ZA---200403713 A 2004ZA-000003713 20040514; IN---200401200 P4 2004IN-CHENP1200 20040601; KR--2005044657 A 2004KR-000708477 20040603; MX--2004005456 A1 2004MX-000005456 20040604; NO---200402673 A 2004NO-000002673 20040625; US-20050065191 A1 2004US-000497363 20041026; DE----60211944 T2 **2002DE-000611944 20021203**; DE----60211944 T2 **2002EP-000792867 20021203**; DE----60211944 T2 **2002WO-EP0013670 20021203**

FDT DE----60211944 E Based on EP-----1453512 A; ES-----2263842 T3 Based on EP-----1453512 A; AU--2002358585 A1 Based on WO--2003047581 A; EP-----1453512 A1 Based on WO--2003047581 A; BR---200214666 A Based on WO--2003047581 A; NZ------533266 A Based on WO--2003047581 A; HU---200402191 A2 Based on WO--2003047581 A; JP--2005514381 W Based on WO--2003047581 A; MX--2004005456 A1 Based on WO--2003047581 A; EP-----1453512 B1 Based on WO--2003047581 A; KR--2005044657 A Based on WO--2003047581 A; EP-----1453512 B8 Based on WO--2003047581 A; DE----60211944 E Based on WO--2003047581 A; AU--2002358585 B2 Based on WO--2003047581 A; DE----60211944 T2 Based on EP-----1453512 A; DE----60211944 T2 Based on WO--2003047581 A

PRAI **2001GB-000028996 20011204**

IC ICM A61K-031/4709; C07C-013/16; C07C-233/18; C07C-271/24; C07D-209/32
ICS A61K-031/32; A61K-031/4035; A61K-031/405; A61K-031/4439; A61K-031/47; A61K-031/497; A61K-031/5377; A61P-025/00; A61P-025/04; A61P-025/14; A61P-025/16; **A61P-025/18**; A61P-025/22; A61P-025/24; A61P-025/28; A61P-025/30; A61P-025/32; A61P-025/34; A61P-025/36; A61P-043/00; C07C-231/12; C07C-233/23; C07C-269/06; C07C-271/16; C07D-209/36; C07D-209/38; C07D-209/44; C07D-215/26; C07D-401/04;

C07D-405/04; C07D-405/06
IPCI A61K-0031/403 [I,C]; A61K-0031/403 [I,C]; A61K-0031/404 [I,A]; A61K-0031/404 [I,A]; A61K-0031/4709 [I,C]; A61K-0031/4709 [I,A]; A61K-0031/4709 [I,A]; A61K-0031/4709 [I,C]; A61P-0025/00 [I,C]; A61P-0025/00 [I,A]; A61P-0025/00 [I,A]; A61P-0025/00 [I,C]; C07C-0233/00 [I,C]; C07C-0233/00 [I,C]; C07C-0233/23 [I,A]; C07C-0233/23 [I,A]; C07C-0271/00 [I,C]; C07C-0271/00 [I,C]; C07C-0271/16 [I,A]; C07C-0271/16 [I,A]; C07C-0271/24 [I,A]; C07C-0271/24 [I,A]; C07C-0271/24 [I,C]; C07D-0209/00 [I,C]; C07D-0209/00 [I,C]; C07D-0209/08 [I,A]; C07D-0209/08 [I,A]; C07D-0209/08 [I,C]; C07D-0209/32 [I,A]; C07D-0209/32 [I,A]; C07D-0209/44 [I,A]; C07D-0209/44 [I,A]; C07D-0209/44 [I,C]; C07D-0215/00 [I,C]; C07D-0215/00 [I,C]; C07D-0215/20 [I,A]; C07D-0215/20 [I,A]; C07D-0405/00 [I,C]; C07D-0405/00 [I,C]; C07D-0405/06 [I,A]; C07D-0405/06 [I,A]; C07D-0405/12 [I,A]; C07D-0405/12 [I,A]; C07D-0405/12 [I,C]; A61K-0031/403 [I,C]; A61K-0031/4709 [I,C]; A61P-0025/00 [I,C]; C07C-0233/00 [I,C]; C07C-0271/00 [I,C]; C07D-0209/00 [I,C]; C07D-0215/00 [I,C]; C07D-0405/00 [I,C]
IPCR A61K-0031/28 [I,C]; A61K-0031/32 [I,A]; A61K-0031/403 [I,C]; A61K-0031/4035 [I,A]; A61K-0031/405 [I,A]; A61K-0031/4427 [I,C]; A61K-0031/4439 [I,A]; A61K-0031/4709 [I,A]; A61K-0031/4709 [I,C]; A61K-0031/4965 [I,C]; A61K-0031/497 [I,A]; A61K-0031/5375 [I,C]; A61K-0031/5377 [I,A]; A61P-0025/00 [I,A]; A61P-0025/00 [I,C]; A61P-0025/04 [I,A]; A61P-0025/14 [I,A]; A61P-0025/16 [I,A]; **A61P-0025/18** [I,A]; A61P-0025/22 [I,A]; A61P-0025/24 [I,A]; A61P-0025/28 [I,A]; A61P-0025/30 [I,A]; A61P-0025/32 [I,A]; A61P-0025/34 [I,A]; A61P-0025/36 [I,A]; A61P-0043/00 [I,A]; A61P-0043/00 [I,C]; C07C-0231/00 [I,C]; C07C-0231/12 [I,A]; C07C-0233/00 [I,C]; C07C-0233/18 [I,A]; C07C-0269/00 [I,C]; C07C-0269/06 [I,A]; C07C-0271/00 [I,C]; C07C-0271/16 [I,A]; C07D-0209/00 [I,C]; C07D-0209/08 [I,A]; C07D-0209/36 [I,A]; C07D-0209/38 [I,A]; C07D-0209/44 [I,A]; C07D-0215/00 [I,C]; C07D-0215/20 [I,A]; C07D-0215/26 [I,A]; C07D-0401/00 [I,C]; C07D-0401/04 [I,A]; C07D-0401/06 [I,A]; C07D-0405/00 [I,C]; C07D-0405/04 [I,A]; C07D-0405/06 [I,A]; C07D-0405/12 [I,A]

AB WO 2003047581 A1 UPAB: 20060202

NOVELTY - Acetylene derivatives (I) are new.

DETAILED DESCRIPTION - Acetylene derivatives of formula (I), their free base or acid addition salt forms are new.

m, n = 0 or 1;

A = OH;

X, Y = H;

A+X and A+Y = a single bond;

Ra = H, 1-4C alkyl, 1-4C alkoxy, trifluoromethyl, halo, cyano, nitro or -COOR1;

R1 = 1-4C alkyl or -COR2;

R2, R4, R5, R7 and R8 = H or 1-4C alkyl;

R = -COR3, -COOR3, -CONR4R5 or -SO2R6;

R3 = phenyl, 2-pyridyl or 2-thienyl (all optionally substituted), 1-4C alkyl or 3-7C cycloalkyl;

R6 = 1-4C alkyl, 3-7C cycloalkyl, or optionally substituted phenyl;

R7+R8 = -CH2-(CH2)p;

p = 0 - 2.

Provided that one of n and p is other than 0; and when m is 1, n is 0, A is OH, X and Y are both H, R is COOEt and R7+R8 is -(CH2)2, then Ra is other than H, trifluoromethyl or methoxy.

INDEPENDENT CLAIMS are included for the following:

(1) preparation of (I);

(2) use of (I) in the manufacture of a composition for treating disorders associated with irregularities of the glutamatergic signal transmission, and of nervous system disorders mediated by human **metabotropic glutamate** receptor (**mGluR5**); and

(3) a combination comprising (I) in free base or acid addition salt form and a second drug substance, for simultaneous or sequential administration.

ACTIVITY - Cerebroprotective; Anticonvulsant; Vasotropic; Relaxant; Analgesic; Tranquilizer; Antiparkinsonian; Nootropic; Neuroprotective; Neuroleptic; Antidepressant; Antipruritic; Antiaddictive.

MECHANISM OF ACTION - Human **metabotropic glutamate** receptor (**mGluR5**) antagonist. Human **metabotropic glutamate** receptor antagonist.

Activity of (I) was evaluated as described in T. Knoepfel et al., Eur. J. Pharmacol. Volume 288, pages 389 - 392 (1994). (I) showed IC50 value of 1 nM - 50 microM. No results for specific compounds are given.

USE - For treating disorders associated with irregularities of the glutamatergic signal transmission, and of nervous system disorders mediated by **mGluR5** (claimed) such as epilepsy, cerebral ischemia (e.g. acute ischemia, ischemic diseases of the eye), muscle spasms (e.g. local or general spasticity), convulsions and pain, acute, traumatic and chronic degenerative processes of the nervous system (e.g. Parkinson's disease, senile dementia, Alzheimer's disease, Huntington's chorea, amyotrophic lateral sclerosis and multiple sclerosis), psychiatric diseases (e.g. schizophrenia and anxiety), depression, itch and drug abuse (e.g. alcohol and nicotine abuse and cocaine use disorders).

ADVANTAGE - (I) exhibits marked and selective modulating, especially antagonistic action at **mGluR5** receptors.

MC CPI: B10-A15; B10-B04; B10-B04B; B12-M05; B14-C01; B14-J01A; B14-J01A1; B14-J01A4; B14-J05A; B14-M01A; B14-M01B; B14-M01C; B14-N17

TECH

ORGANIC CHEMISTRY - Preparation (claimed): Preparation of (I) involves: (a) process (a): (where A is hydroxy), reacting cycloalkanone derivative of formula (II) with 2-aryl acetylene derivative of formula (III); or (b) process (b): (where A+X or A+Y is a single bond), dehydrating a derivative of (I) (where A is OH) and recovering (I) in free base or acid addition salt form.

L20 ANSWER 14 OF 21 WPIX COPYRIGHT 2007 THE THOMSON CORP on STN
AN 2003-449132 [42] WPIX
CR 2003-607838; 2003-618015; 2003-636590; 2003-646033; 2004-330064
DNC C2003-119158 [42]
TI New heteroaryl substituted tetrazole compounds useful for e.g. treatment of acute pain, Alzheimer's disease, schizophrenia, Parkinson's disease, anxiety disorders, epilepsy, drug addiction, and obesity
DC B02; B03
IN CHEN C; COSFORD N D; COSFORD N D P; REGER T; REGER T S; ROPPE J; ROPPE J R; SMITH N; SMITH N D
PA (CHEN-I) CHEN C; (COSF-I) COSFORD N D P; (MERI-C) MERCK & CO INC; (REGE-I) REGER T S; (ROPP-I) ROPPE J R; (SMIT-I) SMITH N D
CYC 99
PI WO--2003029210 A2 20030410 (200342)* EN 60[0]
EP-----1434773 A2 20040707 (200444) EN
AU--2002341921 A1 20030414 (200461) EN
US-20040186295 A1 20040923 (200463) EN
JP--2005508344 W 20050331 (200523) JA 226
ADT WO--2003029210 A2 **2002WO-US0031294 20021001**; US-20040186295 A1 Provisional **2001US-000327132P 20011004**; AU--2002341921 A1 **2002AU-000341921 20021001**; EP-----1434773 A2 **2002EP-000776076 20021001**; EP-----1434773 A2 **2002WO-US0031294 20021001**; US-20040186295 A1 **2002WO-US0031294 20021001**; JP--2005508344 W **2002WO-US0031294 20021001**; JP--2005508344 W **2003JP-000532460 20021001**; US-20040186295 A1 2004US-000491613 20040402
FDT EP-----1434773 A2 Based on WO--2003029210 A; AU--2002341921 A1 Based on WO--2003029210 A; JP--2005508344 W Based on WO--2003029210 A
PRAI **2001US-000327132P 20011004**
2004US-000491613 20040402
IC ICM C07D-00; C07D-401/04
IPCR A61K-0031/135 [I,A]; A61K-0031/135 [I,C]; A61K-0031/4155 [I,A]; A61K-0031/4155 [I,C]; A61K-0031/4164 [I,C]; A61K-0031/4178 [I,A]; A61K-0031/4184 [I,A]; A61K-0031/42 [I,A]; A61K-0031/42 [I,C]; A61K-0031/422 [I,A]; A61K-0031/422 [I,C]; A61K-0031/4427 [I,C]; A61K-0031/4439 [I,A]; A61K-0031/4709 [I,A]; A61K-0031/4709 [I,C]; A61K-0031/472 [I,C]; A61K-0031/4725 [I,A]; A61K-0031/485 [I,A]; A61K-0031/485 [I,C]; A61K-0031/4965 [I,C]; A61K-0031/497 [I,A];

A61K-0045/00 [I,A]; **A61K-0045/00** [I,C]; A61P-0025/00 [I,C]; A61P-0025/04 [I,A]; A61P-0025/08 [I,A]; A61P-0025/14 [I,A]; A61P-0025/16 [I,A]; **A61P-0025/18** [I,A]; A61P-0025/20 [I,A]; A61P-0025/22 [I,A]; A61P-0025/24 [I,A]; A61P-0025/28 [I,A]; A61P-0025/30 [I,A]; A61P-0025/34 [I,A]; A61P-0029/00 [I,A]; A61P-0029/00 [I,C]; A61P-0003/00 [I,C]; A61P-0003/04 [I,A]; C07D-0401/00 [I,C]; C07D-0401/04 [I,A]; C07D-0401/14 [I,A]; C07D-0403/00 [I,C]; C07D-0403/04 [I,A]; C07D-0403/14 [I,A]; C07D-0405/00 [I,C]; C07D-0405/04 [I,A]; C07D-0405/14 [I,A]; C07D-0413/00 [I,C]; C07D-0413/04 [I,A]; C07D-0413/14 [I,A]; C07D-0417/00 [I,C]; C07D-0417/04 [I,A]; C07D-0417/14 [I,A]; C07D-0471/00 [I,C]; C07D-0471/04 [I,A]

AB WO 2003029210 A2 UPAB: 20050903

NOVELTY - Heteroaryl substituted tetrazole compounds (I) are new.

DETAILED DESCRIPTION - Heteroaryl substituted tetrazole compounds of formula (I), or their salts are new.

X = Q (optionally mono-heptasubstituted by Q2);

Q2 = 1-6C alkyl (optionally mono-pentasubstituted by Q1), halo, CN, NO2, 1-6C alkenyl, 1-6C alkynyl, OR1, NR1R2, C(=NR1)NR2R3, N(=NR1)NR2R3, NR1COR2, NR1CO2R2, NR1SO2R4, NR1CONR2R3, SR4, SOR4, SO2R4, SO2NR1R2, COR1, CO2R1, CONR1R2, C(=NR1)R2, or C(=NOR1)R2;

Q2+Q2 = (hetero)cycloalkyl ring fused to X (optionally mono-pentasubstituted by Q1);

Q1 = halo, CN, 1-6C alkyl, O(0-6C alkyl), O(3-7C cycloalkyl), O-(hetero)aryl, N(0-6C alkyl)(0-6C alkyl), N(0-6C alkyl)(3-7C cycloalkyl), or N(0-6C alkyl)(aryl);

Q = (hetero)aryl;

Y = Q (optionally mono-heptasubstituted by Q3);

Q3 = 1-6C alkyl (optionally mono-pentasubstituted by Q1), halo, CN, NO2, 1-6C alkenyl, 1-6C alkynyl, OR5, NR5R6, C(=NR5)NR6R7, N(=NR5)NR6R7, NR5COR6, NR5CO2R6, NR5SO2R8, NR5CONR6R7, -SR8, SOR8, SO2R8, SO2NR5R6, COR5, CO2R5, CONR5R6, C(=NR5)R6, or C(=NOR5)R6;

Q3+Q3 = (hetero)cycloalkyl ring fused to Y (optionally mono-pentasubstituted by Q1);

R1-R3, R5-R7, R9, R10 = 0-6C alkyl, 3-7C cycloalkyl, or (hetero)aryl (all optionally mono-pentasubstituted by Q1);

R4, R8 = 1-6C alkyl, 3-7C cycloalkyl, or (hetero)aryl (all optionally mono-pentasubstituted by Q1);

A = 0-4C alkyl, 0-2C alkyl-SO-(0-2C)alkyl, 0-2C alkyl-SO2-(0-2C)alkyl, 0-2C alkyl-CO-(0-2C)alkyl, 0-2C alkyl-NR9CO-(0-2C)alkyl, 0-2C alkyl-NR9SO2-(0-2C)alkyl or hetero(0-4C)alkyl;

B' = 0-4C alkyl, 0-2C alkyl-SO-(0-2C)alkyl, 0-2C alkyl-SO2-(0-2C)alkyl, 0-2C alkyl-CO-(0-2C)alkyl, 0-2C alkyl-NR10CO-(0-2C)alkyl, 0-2C alkyl-NR10SO2-(0-2C)alkyl or hetero(0-4C)alkyl; and

N = N-oxide.

Provided that at least one of X and Y is a heteroaryl with N adjacent to the position of attachment to A or B' respectively.

An INDEPENDENT CLAIM is also included for a pharmaceutical composition comprising (I) and a carrier.

ACTIVITY - Analgesic; Antiinflammatory; Tranquilizer; Antidepressant; Nootropic; Neuroleptic; Antiaddictive; Neuroprotective; Antiparkinsonian; Anticonvulsant; Vulnerary; Antimicrobial; Anorectic.

MECHANISM OF ACTION - **Metabotropic glutamate** receptor-subtype 5 (**mGluR5**) inhibitor. The activity of 2-(2-(3-chlorophenyl)-2H-tetrazol-5-yl)pyridine (A) against **mGluR5** inhibitor was performed by calcium flux assay. (A) showed an IC50 value of 10 microM.

USE - Compounds of (I) can be used for treating and preventing pain (e.g. acute pain, persistent pain, chronic pain, inflammatory pain, and neuropathic pain), anxiety, depression, bipolar disorder, psychosis, drug withdrawal, tobacco withdrawal, memory loss, cognitive impairment, dementia, Alzheimer's disease, schizophrenia, panic, extrapyramidal motor function (e.g. Parkinson's disease, progressive supramuscular palsy, Huntington's disease, Gilles de la Tourette syndrome, and tardive dyskinesia), anxiety disorders (e.g. panic attack, agoraphobia or specific

phobias, obsessive-compulsive disorder, post-traumatic stress disorder, acute stress disorder, generalized anxiety disorder, eating disorder, substance-induced anxiety disorder, and non-specified anxiety disorder), epilepsy, cognitive dysfunction, drug addiction, circadian rhythm and sleep disorder (e.g. shift-work induced sleep disorder and jet-lag), and obesity (all claimed).

ADVANTAGE - (I) are potent inhibitors of **mGluR5** with minimal side effects.

MC CPI: B04-A04; B05-A01B; B06-F05; B06-H; B07-D03; B07-D04C; B07-D05; B07-D11; B07-D12; B07-D13; B07-H; B10-A04; B10-A09B; B10-B02E; B10-B02G; B10-B04B; B10-C04E; B14-C01; B14-C03; B14-D05C; B14-E11; B14-E12; B14-J01A; B14-J01B; B14-J02C2; B14-J02D3; B14-J03; B14-J04; B14-J07; B14-M01

TECH

ORGANIC CHEMISTRY - Preparation: Preparation of (I) involves reacting an aldehyde moiety of formula (i) with an arylsulfonylhydrazide in a solvent at 0-100 degrees C for 5-60 minutes to form an arylsulfonylhydrazone of formula (ii); and reacting (ii) with an arenediazonium species of formula (iii) in a 1,3-dipolar cycloaddition reaction, followed by purification.

PHARMACEUTICALS - Preferred Composition: The composition further comprises an opiate agonist, opiate antagonist, calcium channel antagonist, 5-hydroxytryptamine (5HT) receptor agonist, 5HT receptor antagonist, sodium channel antagonist, N-methyl-D-aspartate (NMDA) receptor agonist, NMDA receptor antagonist, cyclooxygenase (COX)-2 selective inhibitor, neurokinin (NK)-1 antagonist, non-steroidal anti-inflammatory drug, gamma-aminobutyric acid (GABA)-A receptor modulator, dopamine agonist, dopamine antagonist, selective serotonin reuptake inhibitor, tricyclic antidepressant drug, norepinephrine modulator, L-dihydroxyphenylalanine (DOPA), buspirone, lithium salt, valproate, neurontin, **olanzapine**, nicotinic agonist, nicotinic antagonist, muscarinic agonist, muscarinic antagonist, selective serotonin and norepinephrine reuptake inhibitor (SSNRI), heroin substituting drug (preferably methadone, levo-alpha-acetylmethadol, buprenorphine or naltrexone), disulfiram, or acamprosate.

L20 ANSWER 15 OF 21 WPIX COPYRIGHT 2007 THE THOMSON CORP on STN
AN 2003-183975 [18] WPIX
DNC C2003-048461 [18]
TI Modulating method for casein kinase-I or cyclin-dependent kinase-5 activity in e.g. cells, for treating e.g. epilepsy, comprises treating cells with agent that alters **metabotropic glutamate** receptor intracellular signaling molecule activity
DC B04; D16
IN GREENGARD P; LIU F; NAIRN A C
PA (UYRQ-C) UNIV ROCKEFELLER; (GREE-I) GREENGARD P; (LIUF-I) LIU F; (NAIR-I) NAIRN A C
CYC 99
PI WO--2002102768 A2 20021227 (200318)* EN 98[13] <--
EP-----1404864 A2 20040407 (200425) EN
AU--2002316279 A1 20030102 (200452) EN
JP--2004536597 W 20041209 (200481) JA 166
US-20060223158 A1 20061005 (200666) EN
US-----7129073 B2 20061031 (200672) EN
ADT WO--2002102768 A2 **2002WO-US0019288 20020618**; US-20060223158 A1 Provisional **2001US-000298978P 20010618**; AU--2002316279 A1 **2002AU-000316279 20020618**; EP-----1404864 A2 **2002EP-000746571 20020618**; US-20060223158 A1 **2002US-000175190 20020618**; EP-----1404864 A2 **2002WO-US0019288 20020618**; JP--2004536597 W **2002WO-US0019288 20020618**; JP--2004536597 W **2003JP-000505311 20020618**; US-----7129073 B2 Provisional **2001US-000298978P 20010618**; US-----7129073 B2 **2002US-000175190 20020618**
FDT EP-----1404864 A2 Based on WO--2002102768 A; AU--2002316279 A1 Based on WO--2002102768 A; JP--2004536597 W Based on WO--2002102768 A
PRAI **2001US-000298978P 20010618**
2002US-000175190 20020618

IC ICM C07D--00/; C12N-009/12
IPCI C12N-0009/12 [I,A]; C12N-0009/12 [I,C]; C12Q-0001/48 [I,A]; C12Q-0001/48 [I,C]
IPCR **A61K-0045/00** [I,A]; **A61K-0045/00** [I,C]; A61P-0025/00 [I,C]; A61P-0025/04 [I,A]; A61P-0025/08 [I,A]; A61P-0025/14 [I,A]; A61P-0025/16 [I,A]; **A61P-0025/18** [I,A]; A61P-0025/20 [I,A]; A61P-0025/24 [I,A]; A61P-0025/28 [I,A]; A61P-0025/30 [I,A]; A61P-0025/36 [I,A]; A61P-0029/00 [I,A]; A61P-0029/00 [I,C]; A61P-0035/00 [I,A]; A61P-0035/00 [I,C]; A61P-0043/00 [I,A]; A61P-0043/00 [I,C]; C12N-0015/09 [I,A]; C12N-0015/09 [I,C]; C12N-0009/12 [I,A]; C12N-0009/12 [I,C]; C12Q-0001/02 [I,A]; C12Q-0001/02 [I,C]; C12Q-0001/48 [I,A]; C12Q-0001/48 [I,C]
AB WO 2002102768 A2 UPAB: 20050528

NOVELTY - New method of modulating (M1) casein kinase-I (CKI) activity or cyclin-dependent kinase-5 (Cdk5) activity in a cell or tissue, comprises contacting the cell or tissue with an effective amount of a compound that alters the activity of a **metabotropic glutamate** receptor intracellular signaling molecule.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for:

(1) a method of identifying (M2) a compound that modulates the activity of CKI and/or Cdk5 in a cell or tissue of interest comprising:

(a) determining a first level of CKI and/or Cdk5 activity in the cell or tissue;

(b) contacting the cell or tissue with a test compound; and

(c) determining a second level of CKI and/or Cdk5 activity in the cell or tissue, where a difference in the first level and the second level of CKI and/or Cdk5 activity indicates the ability of the test compound to modulate CKI and/or Cdk5 activity;

(2) a method of identifying (M3) a compound for modulating activity of calcium channels in cell or tissue of interest comprising:

(a) determining a first level of CKI and/or Cdk5 activity in a cell or tissue of interest;

(b) determining a first level of calcium channel activity in the cell or tissue;

(c) contacting the cell or tissue with a test compound, determining a second level of CKI and/or Cdk5 activity in the cell or tissue; and

(d) determining a second level of calcium channel activity in the cell or tissue, where a difference in the first level and the second level of CKI and/or Cdk5 activity and a difference in the first level and the second level of calcium channel activity are indicative of the ability of the test compound to modulate the activity of calcium channels;

(3) a method of regulating activity of calcium channels in a cell, comprising administering an effective amount of a compound that modulates activity of CKI or Cdk5; and

(4) a method of treating a disorder characterized by an increase or a decrease in calcium channel activity, comprising administering an effective amount of a compound that modulates the activity of CKI or Cdk5.

ACTIVITY - Nootropic; Neuroprotective; Anticonvulsant; Antiparkinsonian; Neuroleptic; Cerebroprotective; Antidepressant; Tranquilizer; Analgesic; Cytostatic; Antiaddictive.

No supporting data is given.

MECHANISM OF ACTION - CKI Activity or Cdk5 Activity Modulator; Calcium Channel Activity Regulator (claimed); **Metabotropic Glutamate** Receptor (**mGluR**) Agonist or Antagonist.

USE - (M1) is useful for modulating CKI activity or Cdk5 activity in a cell or tissue which is useful for regulating activity of calcium channels in a cell, especially neuron (claimed). The compounds identified by (M2) and (M3) are useful for treating **mGluR**-related, CKI-related, Cdk5-related or calcium channel-related disorder such as Alzheimer's disease, Huntington's Disease, Parkinson's disease, Tourette's syndrome, stroke, epilepsy, schizophrenia, insomnia, depression, attention deficit disorder (ADD), attention deficit hyperactivity disorder (ADHD), drug abuse, pain, and cancer.

MC CPI: B04-F01; B04-L04; B04-L05A; B11-C07; B11-C08E; B11-C10; B12-K04A; B14-C01; B14-D06; B14-F02D1; B14-H01; B14-J01A; B14-J01B; B14-J07; B14-L01; B14-L06; B14-M01C; B14-N16; D05-H02; D05-H08; D05-H09;

D05-H17A4

TECH

BIOTECHNOLOGY - Preferred Method: In (M1), the compound modulates the phosphorylation of an inhibitory autophosphorylation site on a CKI. The CKI is CKIepsilon, CKIalpha, CKIdelta or CKIgamma. The **metabotropic glutamate** receptor intracellular signaling molecule is PLCbeta, calcineurin, PP1 or P2A. The compound that alters the activity of the **metabotropic glutamate** receptor intracellular signaling molecule is a **metabotropic glutamate** receptor agonist or antagonist, where contact of the cell or tissue with the agonist increases the activity of CKI or Cdk5, or with the antagonist decreases the activity of CKI or Cdk5.

L20 ANSWER 16 OF 21 WPIX COPYRIGHT 2007 THE THOMSON CORP on STN
AN 2003-148379 [14] WPIX
DNC C2003-038301 [14]
TI Use of new and known imidazo(1,2-a)-pyridine derivatives for treating **metabotropic glutamate** receptor **mGlu5** mediated disorders e.g. Alzheimer's disease, anxiety, depression and Parkinson's disease
DC B02
IN MUTEL V; PETERS J; PETERS J U; WICHMANN J
PA (HOFF-C) HOFFMANN LA ROCHE & CO AG F; (HOFF-C) HOFFMANN LA ROCHE INC; (MUTE-I) MUTEL V; (PETE-I) PETERS J; (WICH-I) WICHMANN J
CYC 97
PI WO--2002092086 A1 20021121 (200314)* EN 16[0] <--
US-20020188128 A1 20021212 (200314) EN <--
US-----6596731 B2 20030722 (200354) EN
US-20030212096 A1 20031113 (200382) EN
EP-----1381363 A1 20040121 (200410) EN
KR--2003083013 A 20031023 (200415) KO
BR---200208387 A 20040615 (200440) PT
AU--2002312768 A1 20021125 (200452) EN <--
JP--2004525192 W 20040819 (200455) JA 58
US-20040180921 A1 20040916 (200461) EN
MX--2003008525 A1 20040101 (200471) ES
EP-----1381363 B1 20041208 (200480) EN
CN-----1529597 A 20040915 (200501) ZH
DE----60202200 E 20050113 (200506) DE
ZA---200306341 A 20050126 (200513) EN 43
US-----6861437 B2 20050301 (200516) EN
ES-----2232756 T3 20050601 (200538) ES
US-----6916826 B2 20050712 (200546) EN
DE----60202200 T2 20051215 (200582) DE
MX------234339 B 20060213 (200649) ES
KR------557847 B1 20060310 (200724) KO
ADT WO--2002092086 A1 **2002WO-EP0003098 20020320**; US-20020188128 A1 **2002US-000093790 20020308**; US-----6596731 B2 **2002US-000093790 20020308**; US-20030212096 A1 Div Ex **2002US-000093790 20020308**; US-20040180921 A1 Div Ex **2002US-000093790 20020308**; US-----6861437 B2 Div Ex **2002US-000093790 20020308**; US-----6916826 B2 Div Ex **2002US-000093790 20020308**; AU--2002312768 A1 **2002AU-000312768 20020320**; BR---200208387 A **2002BR-000008387 20020320**; CN-----1529597 A **2002CN-000807354 20020320**; DE----60202200 E **2002DE-000602200 20020320**; DE----60202200 T2 **2002DE-000602200 20020320**; EP-----1381363 A1 **2002EP-000737889 20020320**; EP-----1381363 B1 **2002EP-000737889 20020320**; DE----60202200 E **2002EP-000737889 20020320**; ES-----2232756 T3 **2002EP-000737889 20020320**; DE----60202200 T2 **2002EP-000737889 20020320**; JP--2004525192 W **2002JP-000589003 20020320**; EP-----1381363 A1 **2002WO-EP0003098 20020320**; BR---200208387 A **2002WO-EP0003098 20020320**; JP--2004525192 W **2002WO-EP0003098 20020320**; MX--2003008525 A1 **2002WO-EP0003098 20020320**; EP-----1381363 B1

2002WO-EP0003098 20020320; DE----60202200 E **2002WO-EP0003098 20020320**; DE----60202200 T2 **2002WO-EP0003098 20020320**; MX------234339 B **2002WO-EP0003098 20020320**; US-20030212096 A1 2003US-000407928 20030404; US-20040180921 A1 Div Ex 2003US-000407928 20030404; US-----6861437 B2 2003US-000407928 20030404; US-----6916826 B2 Div Ex 2003US-000407928 20030404; ZA---200306341 A 2003ZA-000006341 20030814; MX--2003008525 A1 2003MX-000008525 20030919; MX------234339 B 2003MX-000008525 20030919; KR--2003083013 A 2003KR-000712535 20030926; US-20040180921 A1 2004US-000809068 20040325; US-----6916826 B2 2004US-000809068 20040325; KR------557847 B1 **2002WO-EP0003098 20020320**; KR------557847 B1 2003KR-000712535 20030926

FDT DE----60202200 E Based on EP-----1381363 A; ES-----2232756 T3 Based on EP-----1381363 A; DE----60202200 T2 Based on EP-----1381363 A; US-20030212096 A1 Div ex US-----6596731 B; US-20040180921 A1 Div ex US-----6596731 B; US-----6861437 B2 Div ex US-----6596731 B; US-----6916826 B2 Div ex US-----6596731 B; EP-----1381363 A1 Based on WO--2002092086 A; BR---200208387 A Based on WO--2002092086 A; AU--2002312768 A1 Based on WO--2002092086 A; JP--2004525192 W Based on WO--2002092086 A; MX--2003008525 A1 Based on WO--2002092086 A; EP-----1381363 B1 Based on WO--2002092086 A; DE----60202200 E Based on WO--2002092086 A; DE----60202200 T2 Based on WO--2002092086 A; MX------234339 B Based on WO--2002092086 A; KR------557847 B1 Previous Publ KR--2003083013 A; KR------557847 B1 Based on WO--2002092086 A

PRAI **2001EP-000107562 20010327**

IC ICM A61K-031/437; C07D-471/04
ICS A61P-021/04; A61P-025/00; A61P-025/08; A61P-025/14; A61P-025/16; **A61P-025/18**; A61P-025/22; A61P-025/24; A61P-025/28; A61P-043/00; A61P-009/10

IPCI A61K-0031/4353 [I,C]; A61K-0031/437 [I,A]; A61P-0025/00 [I,A]; C07D-0471/00 [I,C]; C07D-0471/04 [I,A]

IPCR A61K-0031/4353 [I,C]; A61K-0031/437 [I,A]; A61P-0021/00 [I,C]; A61P-0021/04 [I,A]; A61P-0025/00 [I,A]; A61P-0025/00 [I,C]; A61P-0025/08 [I,A]; A61P-0025/14 [I,A]; A61P-0025/16 [I,A]; **A61P-0025/18** [I,A]; A61P-0025/22 [I,A]; A61P-0025/24 [I,A]; A61P-0025/28 [I,A]; A61P-0043/00 [I,A]; A61P-0043/00 [I,C]; A61P-0009/00 [I,C]; A61P-0009/10 [I,A]; C07D-0471/00 [I,C]; C07D-0471/04 [I,A]

AB WO 2002092086 A1 UPAB: 20060202

NOVELTY - Imidazo(1,2-a)-pyridine derivatives (I) are used for treating or preventing **metabotropic glutamate** receptor **mGluR5** mediated disorders.

DETAILED DESCRIPTION - Imidazo(1,2-a)-pyridine derivatives of formula (I) or their salts are used for treating or preventing **mGluR5** receptor mediated disorders.

R1, R2 = H, 1-6C alkyl, halo, OH or 1-6C alkoxy;

A = aryl or heteroaryl (both optionally substituted by at least one of T) or a group of formula (i);

T = 1-6C alkyl, halo, 1-6C haloalkyl, OH, 1-6C alkoxy, benzyloxy, amino, 1-6C alkylamino, di-(1-6C)alkylamino, arylamino, diarylamino or NO2;

X = CH2 or O, and

n = 1 or 2.

An INDEPENDENT CLAIM is included for the following new compounds: 7-chloro-2-(3,4-dimethylphenyl)-imidazo(1,2-a)pyridine (Ia), 2-(3,4-dimethoxyphenyl)-imidazo(1,2-a)pyridine, 2-(3,4-dimethylphenyl)-7-methoxy-imidazo(1,2-a)pyridine, 2-(3,4-dimethoxyphenyl)-7-methoxy-imidazo(1,2-a)pyridine, 2-(3,4-dimethylphenyl)-7-methyl-imidazo(1,2-a)pyridine, 2-(3-bromo-4-fluorophenyl)-imidazo(1,2-a)pyridine, 2-(4-benzyloxy-3-methoxyphenyl)-imidazo(1,2-a)pyridine, 2-indan-5-yl-imidazo(1,2-a)pyridine, 2-(3-bromophenyl)-imidazo(1,2-a)pyridine, 2-(3-iodophenyl)-imidazo(1,2-a)pyridine, 2-(3-methylphenyl)-imidazo(1,2-a)pyridine, 2-benzo(b)thiophene-3-yl-imidazo(1,2-a)pyridine, 2-(3-trifluoromethylphenyl)-imidazo(1,2-a)pyridine, 2-(2,3-dihydrobenzofuran-5-yl)-imidazo(1,2-a)pyridine, 2-(3-fluorophenyl)-imidazo(1,2-a)pyridine, 2-(3,4-dimethylphenyl)-7-ethylimidazo(1,2-a)pyridine, 2-(5-methylthiophene-2-yl)-imidazo(1,2-a)pyridine, 2-(2,5-dimethoxythiophene-3-yl)-imidazo(1,2-a)pyridine or

2-(3,4-dimethoxyphenyl)-6-methyl-imidazo(1,2-a)pyridine.

ACTIVITY - Nootropic; Neuroprotective; Antiparkinsonian; Vasotropic; Anticonvulsant; Neuroleptic; Antidepressant; Tranquilizer; Analgesic; Antimigraine; Antiemetic; Antidiabetic; Anti-HIV; Ophthalmological; Antismoking; Cardiant.

MECHANISM OF ACTION - **mGluR5** antagonist.

In a test, cDNA encoding rat **mGlu5a** receptor was transiently transfected into EBNA cells using a procedure as described in E.J. Schlager and K. Christensen (Transient gene expression in mammalian cells grown in serum-free suspension culture, cytotechnology 1999, 30, 71-83). (Ca2+)i measurements were performed on **mGlu5a** transfected EBNA cells after incubation of the cells with Fluo 3-AM for 1 hour at 37degreesC followed by 4 washes with assay buffer. Results showed that 7-chloro-2-(3,4-dimethyl)-imidazo(1,2-a)pyridine (Ia) exhibited an IC50 value of 0.1 micro-M as an **mGluR5** antagonist.

USE - Used for treating or preventing acute and/or chronic neurological disorders, cognitive disorders and memory deficits such as Alzheimer's disease, senile dementia, Parkinson's disease, ischemia, Huntington's chorea, amyotrophic lateral sclerosis, multiple sclerosis, psychiatric diseases (such as psychosis, epilepsy, schizophrenia, anxiety, depression) and acute and chronic pain (all claimed), dementia caused by AIDS, eye injuries, retinopathy, iodopathic parkinsonism, parkinsonism caused by medicaments and conditions which lead to glutamate-deficient functions e.g. muscle spasm, convulsions, migraine, urinary incontinence, nicotine addiction, psychoses, opiate addiction, vomiting and dyskinesia, restricted brain function caused by bypass operations or transplants, poor blood supply to the brain, spinal cord injuries, head injuries, hypoxia caused by pregnancy, cardiac arrest and hypoglycaemia.

MC CPI: B06-D05; B14-C01; B14-E05; B14-F01B; B14-F10; B14-J01A1; B14-J01A3; B14-J01A4; B14-J01B3; B14-J01B4; B14-J05A; B14-J07; B14-L06; B14-M01B; B14-M01C; B14-N03; B14-N07D; B14-N16; B14-S01

TECH

ORGANIC CHEMISTRY - Preparation: Preparation of (I) comprises reacting a 2-aminopyridine compound of formula (II) with Br-CH2-CO-A.

L20 ANSWER 17 OF 21 WPIX COPYRIGHT 2007 THE THOMSON CORP on STN
AN 2003-092873 [08] WPIX
DNC C2003-023137 [08]
TI New method of treating or preventing a neurological disorder e.g. Fragile X, autism, mental retardation, schizophrenia and Downs' syndrome comprises administering Group I **metabotropic glutamate** receptor (**mGluR**) antagonist
DC B05
IN BEAR F; BEAR M F; HUBER K M; HUBER M; WARREN S T
PA (BEAR-I) BEAR M F; (HUBE-I) HUBER K M; (UYBR-N) UNIV BROWN; (UYBR-N) UNIV BROWN RES FOUND; (UYBR-N) UNIV BROWN RES FOUND BURF; (UYEM-N) UNIV EMORY; (WARR-I) WARREN S T
CYC 99
PI WO--2002078745 A2 20021010 (200308)* EN 81[9] <--
US-20030100539 A1 20030529 (200337) EN
EP-----1392363 A2 20040303 (200417) EN
US-20040067978 A1 20040408 (200426) EN
AU--2002307049 A1 20021015 (200432) EN <--
JP--2005500260 W 20050106 (200505) JA 143
US-----6890931 B2 20050510 (200532) EN
US-----6916821 B2 20050712 (200546) EN
US-20050171067 A1 20050804 (200552) EN
AU--2002307049 A8 20051006 (200612) EN
DE----60214846 E 20061102 (200675) DE
ES-----2272754 T3 20070501 (200731) ES
DE----60214846 T2 20070516 (200734) DE
ADT WO--2002078745 A2 **2002WO-US0010211 20020402**; US-20030100539 A1
Provisional **2001US-000280915P 20010402**; US-20040067978 A1
Provisional **2001US-000280915P 20010402**; US-----6890931 B2
Provisional **2001US-000280915P 20010402**; US-----6916821 B2
Provisional **2001US-000280915P 20010402**; US-20050171067 A1

Provisional **2001US-000280915P 20010402**; AU--2002307049 A1
2002AU-000307049 20020402; AU--2002307049 A8
2002AU-000307049 20020402; DE----60214846 E **2002DE-000614846**
20020402; EP-----1392363 A2 **2002EP-000757930 20020402**;
DE----60214846 E **2002EP-000757930 20020402**; ES-----2272754 T3
2002EP-000757930 20020402; JP--2005500260 W **2002JP-000577009**
20020402; US-20030100539 A1 **2002US-000114433 20020402**;
US-20040067978 A1 CIP of **2002US-000114433 20020402**;
US-----6890931 B2 **2002US-000114433 20020402**; US-----6916821 B2
CIP of **2002US-000114433 20020402**; US-20050171067 A1 CIP of
2002US-000114433 20020402; EP-----1392363 A2
2002WO-US0010211 20020402; US-20040067978 A1 CIP of
2002WO-US0010211 20020402; JP--2005500260 W **2002WO-US0010211**
20020402; US-----6916821 B2 CIP of **2002WO-US0010211 20020402**
; US-20050171067 A1 CIP of **2002WO-US0010211 20020402**;
DE----60214846 E **2002WO-US0010211 20020402**; US-20040067978 A1
2003US-000408771 20030404; US-----6916821 B2 2003US-000408771 20030404;
US-20050171067 A1 Cont of 2003US-000408771 20030404; US-20050171067 A1
2004US-000015328 20041217; DE----60214846 T2 **2002DE-000614846**
20020402; DE----60214846 T2 **2002EP-000757930 20020402**;
DE----60214846 T2 **2002WO-US0010211 20020402**

FDT DE----60214846 E Based on EP-----1392363 A; ES-----2272754 T3 Based on EP-----1392363 A; US-20050171067 A1 CIP of US-----6890931 B; EP-----1392363 A2 Based on WO--2002078745 A; AU--2002307049 A1 Based on WO--2002078745 A; JP--2005500260 W Based on WO--2002078745 A; AU--2002307049 A8 Based on WO--2002078745 A; DE----60214846 E Based on WO--2002078745 A; DE----60214846 T2 Based on EP-----1392363 A; DE----60214846 T2 Based on WO--2002078745 A

PRAI **2001US-000280915P 20010402**
2002WO-US0010211 20020402
2002US-000114433 20020402
2003US-000408771 20030404
2004US-000015328 20041217

IC ICM **A61K-045/00**; **A61K-045/08**
ICS A61K-031/198; A61K-031/44; A61K-031/472; A61K-031/4725; A61P-025/00; **A61P-025/18**; A61P-025/28; A61P-043/00

IPCI A61K-0031/185 [I,C]; A61K-0031/185 [I,C]; A61K-0031/198 [I,A]; A61K-0031/44 [I,A]; A61K-0031/44 [I,C]; A61K-0031/472 [I,A]; A61K-0031/472 [I,C]; A61K-0031/4725 [I,A]; **A61K-0045/00** [I,C]; **A61K-0045/00** [I,C]; **A61K-0045/08** [I,A]; A61P-0025/00 [I,A]; A61P-0025/00 [I,C]; **A61P-0025/18** [I,A]; A61P-0025/28 [I,A]; A61P-0043/00 [I,A]; A61P-0043/00 [I,C]; A61K-0031/185 [I,C]; A61K-0031/198 [I,A]; A61K-0031/44 [I,A]; A61K-0031/44 [I,C]; A61K-0031/472 [I,A]; A61K-0031/472 [I,C]; A61K-0031/4725 [I,A]; **A61K-0045/00** [I,C]; **A61K-0045/08** [I,A]; A61P-0025/00 [I,A]; A61P-0025/00 [I,C]; **A61P-0025/18** [I,A]; A61P-0025/28 [I,A]; A61P-0043/00 [I,A]; A61P-0043/00 [I,C]

IPCR A61K-0031/00 [I,A]; A61K-0031/00 [I,C]; A61K-0031/185 [I,C]; A61K-0031/198 [I,A]; A61K-0031/44 [I,A]; A61K-0031/44 [I,C]; A61K-0031/472 [I,A]; A61K-0031/472 [I,C]; A61K-0031/4725 [I,A]; **A61K-0045/00** [I,A]; **A61K-0045/00** [I,C]; **A61K-0045/08** [I,A]; A61P-0025/00 [I,A]; A61P-0025/00 [I,C]; **A61P-0025/18** [I,A]; A61P-0025/28 [I,A]; A61P-0043/00 [I,A]; A61P-0043/00 [I,C]; C07D-0213/00 [I,C]; C07D-0213/16 [I,A]; C07D-0213/76 [I,A]; C07D-0217/00 [I,C]; C07D-0217/26 [I,A]; C07D-0401/00 [I,C]; C07D-0401/12 [I,A]

AB WO 2002078745 A2 UPAB: 20060118

NOVELTY - New method of treating, preventing or lessening the severity of a neurological disorder selected from Fragile X, autism, mental retardation, schizophrenia and Downs' syndrome comprises administering a Group I **metabotropic glutamate** receptor (**mGluR**) antagonist.

DETAILED DESCRIPTION - An INDEPENDENT CLAIM is also included for a kit (A) comprising at least one Group I **mGluR** antagonist, provided in single oral dosage form or as a transdermal patch with instructions (written and/or pictorial) describing the use of the kit, and optionally warnings of possible side effects and drug-drug or drug-food

interactions.

ACTIVITY - Nootropic; Neuroleptic.

MECHANISM OF ACTION - **Metabotropic glutamate** receptor (**mGluR**) antagonist binder.

To examine the effect of **metabotropic glutamate** receptor (**mGluR**) activation on alpha-amino-3-hydroxy-5-methylisoxazole-4-propionate receptor (AMPARs) expressed on the surface of hippocampal neurons, an acid-strip immunocytochemical staining protocol was used. Surface receptors on living cultured hippocampal neurons were labeled with antibodies directed against the extracellular N-terminus of the GluR1 subunit. The cells were treated with either (RS)-3,5-dihydroxyphenylglycine (DHPG) (50 microM, 5 minutes) or control medium and after various intervals, the remaining surface antibodies were stripped away with an acetic acid wash. The neurons were fixed and immunocytochemistry was done under membrane-permeabilizing conditions to detect antibodies bound to internalized AMPARs.

DHPG application for 5 minutes stimulated a greater than 2-fold increase in internalized GluR1 puncta that was observed as early as 15 minutes after treatment onset (puncta per 10 microl of dendrite, control, 0.62:1+/-0.09, n = 65 cells; DHPG, 1.44:1+/-0.17, n = 60 cells; p less than 0.0002) and persisted for at least 1 hour (control, 0.58:1+/-0.08, n = 42 cells; DHPG, 1.14+/-0.15, n = 38 cells). The increased internalization of GluR1 was a specific consequence of activating groups I **mGluR**, as it was completely blocked by the **mGluR** antagonist LY344545. In contrast, the N-methyl-D-aspartate receptors (NMDAR) antagonist 2-amino-5-phosphonovaleric acid (APV) (50 microM) had no effect (control, 0.74+/-0.19, n = 7; DHPG, 1.49+/-0.22, n = 10; DHPG+APV, 1.51+/-0.3, n = 10).

USE - For treating, preventing or lessening the severity of a neurological disorder such as Fragile X, autism, mental retardation, schizophrenia and Down's syndrome. The kit may be used for conducting a pharmaceutical business by marketing to healthcare providers the benefits of using the kit; providing instruction material to patients or physicians for using the kit; determining an appropriate dosage of an **mGluR** antagonist to treat neurological disorder in a patients by conducting therapeutic profiling of formulations of the **mGluR** antagonist for efficacy and toxicity in animals; providing a distribution network for selling a kit or the formulation, by licensing, to a third party, the rights for further development and sale of the **mGluR** antagonist for treating neurological disorder or additionally providing a sales group for marketing the preparation to healthcare providers (all claimed).

ADVANTAGE - The **mGluR** antagonist has an ED50 for **mGluR5** antagonism of at least 10 times less than that for **mGluR1** and at least 100 times less than the ED50 for antagonism of ionotropic glutamate receptors. The **mGluR** antagonist has an ED50 of at most1 microM (preferably at most100 nM) and has a therapeutic index (TI) of at least10 (preferably at least100) (all claimed).

MC CPI: B06-D03; B07-D04C; B10-B02E; B11-C08; B11-C09; B12-K04E; B12-M02F; B12-M07; B12-M11; B14-J01A; B14-J01A4; B14-J01B; B14-L06

TECH

PHARMACEUTICALS - Preferred Method: The **mGluR** antagonist binds to a **mGluR** receptor (preferably to an intracellular G protein involved in **mGluR** receptor signal transduction).
Preferred Kit: In (A), the Group I **mGluR** antagonist is preferably a selective **mGluR5** antagonist.

L20 ANSWER 18 OF 21 WPIX COPYRIGHT 2007 THE THOMSON CORP on STN
AN 2002-010897 [01] WPIX
DNC C2002-002721 [01]
DNN N2002-009063 [01]
TI New multi-protein complexes, useful for identifying compounds useful in the treatment of conditions associated with dysfunction of N-methyl-D-aspartate receptors, e.g. learning impairment, psychiatric disorders or neurological disorders
DC B04; D16; S03
IN GRANT S G N; GRANT S G N D O N; HUSI H; HUSI H D O N

PA (GRAN-I) GRANT S G N; (HUSI-I) HUSI H; (UYED-N) UNIV EDINBURGH
CYC 94
PI WO--2001077170 A2 20011018 (200201)* EN 202[25] <--
AU---200144411 A 20011023 (200213) EN <--
EP-----1272517 A2 20030108 (200311) EN
US-20030176651 A1 20030918 (200362) EN
JP--2003530125 W 20031014 (200368) JA 198
ADT WO--2001077170 A2 **2001WO-GB0001570 20010406**; AU---200144411 A **2001AU-000044411 20010406**; EP-----1272517 A2 **2001EP-000917331 20010406**; JP--2003530125 W **2001JP-000575640 20010406**; EP-----1272517 A2 **2001WO-GB0001570 20010406**; US-20030176651 A1 **2001WO-GB0001570 20010406**; JP--2003530125 W **2001WO-GB0001570 20010406**; US-20030176651 A1 2003US-000240873 20030310
FDT AU---200144411 A Based on WO--2001077170 A; EP-----1272517 A2 Based on WO--2001077170 A; JP--2003530125 W Based on WO--2001077170 A
PRAI **2000GB-000008321 20000406**
IC ICM C12N-015/09
ICS G01N-030/48
IPCR A61K-0038/00 [N,A]; A61K-0038/00 [N,C]; **A61K-0045/00** [I,A]; **A61K-0045/00** [I,C]; A61P-0025/00 [I,A]; A61P-0025/00 [I,C]; **A61P-0025/18** [I,A]; A61P-0025/20 [I,A]; A61P-0025/28 [I,A]; A61P-0009/00 [I,A]; A61P-0009/00 [I,C]; B01J-0020/281 [I,A]; B01J-0020/281 [I,C]; C07K-0001/00 [I,A]; C07K-0001/00 [I,C]; C07K-0001/22 [I,A]; C07K-0014/435 [I,C]; C07K-0014/47 [I,A]; C07K-0014/705 [I,A]; C12N-0015/09 [I,A]; C12N-0015/09 [I,C]; C12N-0015/12 [I,A]; C12N-0015/12 [I,C]; C12N-0005/10 [I,A]; C12N-0005/10 [I,C]; C12Q-0001/68 [I,A]; C12Q-0001/68 [I,C]; G01N-0030/00 [I,C]; G01N-0030/88 [I,A]; G01N-0033/15 [I,A]; G01N-0033/15 [I,C]; G01N-0033/50 [I,A]; G01N-0033/50 [I,C]; G01N-0033/53 [I,A]; G01N-0033/53 [I,C]; G01N-0033/566 [I,A]; G01N-0033/566 [I,C]; G01N-0033/68 [I,A]; G01N-0033/68 [I,C]
AB WO 2001077170 A2 UPAB: 20050524
NOVELTY - A multi-protein complex comprising the polypeptide subunit NR1 and at least one other specified protein, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) a sub-complex comprising 2 or more proteins from the selected groups;

(2) producing the multi-protein component comprising contacting central nervous system tissue with a peptide that binds to the specified proteins;

(3) producing the multi-protein component comprising contacting central nervous system tissue with a molecule that binds to the proteins in the first group;

(4) making the sub-complex comprising separately expressing and isolating genetic constructs encoding components selected from the groups and mixing the components;

(5) host cells for use in the method of (4);

(6) sub-cellular fractions isolated from cells containing a multi-protein complex;

(7) making the sub-complex comprising contacting the novel complex with an agent that interferes with protein-protein interactions and isolating the sub-complex formed;

(8) identifying a candidate compound for treating conditions associated with dysfunction of N-methyl-D-aspartate (NMDA) receptors comprising determining if the test compound interacts with the novel complex;

(9) compounds obtained by the identification method;

(10) treating a patient with learning impairment, psychiatric disorders or neurological disorders comprising administration of the compound;

(11) diagnosing and prognosing conditions associated with dysfunction of NMDA receptors; and

(12) determining the susceptibility of a patient to conditions associated with dysfunction of NMDA receptors.

ACTIVITY - Neuroleptic; cerebroprotective; anticonvulsant.

No biological data is given.
MECHANISM OF ACTION - None given.
USE - The complex is useful for identifying compounds useful in the treatment of conditions associated with dysfunction of NMDA receptors, e.g. learning impairment, psychiatric disorders or neurological disorders, especially schizophrenia, stroke and epilepsy.

MC CPI: B04-F0100E; B04-N04; B11-C07B; B12-K04E; B14-J01B3; B14-N16; D05-H09; D05-H14; D05-H17C
EPI: S03-E14H

TECH
BIOLOGY - Preferred Complex: The complex includes at least six components from the first or second groups and may includes all of the components. It may be obtained by peptide affinity chromatography of central nervous system tissue. The complex may be obtained from tissue obtained from the brain, especially the forebrain.
ORGANIC CHEMISTRY - Preferred Components: The other protein is selected from **mGluR1alpha**, N-ethylmaleimide-sensitive factor (NSF), Homer/Ves1-1, Shank, AKAP-150/79, SAP97, protein kinase (PK)A-R2beta, PKC-beta, PKC-gamma, PKC-epsilon, PP2A, PP5, PTP1D (SHP2), PP1, PP2B, PYK2, extracellular signal-regulated kinase (ERK)1, EKR2, MEK1, MEK2, Mitogen activated protein (MAP) kinase phosphatase (MKP)2, Rsk-2, c-RaF1, Rac1, Rap2, Ras, NF1GRP, Ra1A, phosphotidylinositol (PI)3 kinase, phospholipase (PL)Cgamma, cPLA2, arg3.1, N-Cadherin, beta-catenin, Desmoglein, L1, pp120CAS, Myosin, Dynamin, Clathrin heavy chain, HSP70, Tubulin, Cortactin, CortBP-1, Bassoon, Myosin B heavy chain, P53 binding protein 1, Tight junction protein ZO-1, Est525.7 hypothetical 97.8 kDa protein, Sarcolemmal associated protein-3, HSP70-like, HS71 protein, Kinesin light chain 2, a-Internexin, RNA binding protein FUS/TLS, Phosphofructokinase, Est700.75, Est763.26, Est536.68, Est621.15, Est571.14 or Est762.20. The second group of proteins includes NR1, NR2A, NR2B, NR2C, NR2D, NR3, GluR6, GluR7, PSD-95, ChapSyn110/PSD-93, Sap102, GKAP/SAPAP, Yotiao, PKA catalytic subunit, CaM kinase 11beta, Src, Fyn, SynGAP, Calmodulin, NNOS, Citron, MAP2B, Actin, alpha-actinin or Spectrin.

L20 ANSWER 19 OF 21 WPIX COPYRIGHT 2007 THE THOMSON CORP on STN
AN 2001-616433 [71] WPIX
DNC C2001-184579 [71]
TI Use of a compound which inhibits activity or activation of **metabotropic glutamate** receptors for the manufacture of a medicament for treating movement disorders, e.g. disorders related to parkinsonism, with reduced side effects
DC B05
IN BROTCHIE J; CROSSMAN A; HILL M
PA (BROT-I) BROTCHIE J; (CROS-I) CROSSMAN A; (HILL-I) HILL M; (MOTA-N) MOTAC NEUROSCIENCE LTD; (UYMA-N) UNIV VICTORIA MANCHESTER
CYC 94
PI WO--2001072291 A2 20011004 (200171)* EN 24[4] <--
AU---200142568 A 20011008 (200208) EN <--
EP-----1274417 A2 20030115 (200306) EN
US-20030109504 A1 20030612 (200340) EN
JP--2003528136 W 20030924 (200365) JA 33
AU--2001242568 B2 20041104 (200504) EN
ADT WO--2001072291 A2 **2001WO-GB0001279 20010323**; AU---200142568 A **2001AU-000042568 20010323**; AU--2001242568 B2 **2001AU-000242568 20010323**; EP-----1274417 A2 **2001EP-000915476 20010323**; JP--2003528136 W **2001JP-000570252 20010323**; EP-----1274417 A2 **2001WO-GB0001279 20010323**; US-20030109504 A1 **2001WO-GB0001279 20010323**; JP--2003528136 W **2001WO-GB0001279 20010323**; US-20030109504 A1 **2002US-000239710 20021114**
FDT AU--2001242568 B2 Previous Publ AU---200142568 A; AU---200142568 A Based on WO--2001072291 A; EP-----1274417 A2 Based on WO--2001072291 A; JP--2003528136 W Based on WO--2001072291 A; AU--2001242568 B2 Based on WO--2001072291 A
PRAI **2000GB-000007193 20000325**
IC ICM **A61K-045/00**

IPCR A61K-0031/00 [I,A]; A61K-0031/00 [I,C]; A61K-0031/185 [I,C]; A61K-0031/192 [I,A]; A61K-0031/196 [I,A]; A61K-0031/198 [I,A]; A61K-0031/352 [I,C]; A61K-0031/353 [I,A]; A61K-0031/4353 [I,C]; A61K-0031/437 [I,A]; A61K-0031/44 [I,A]; A61K-0031/44 [I,C]; A61K-0031/47 [I,A]; A61K-0031/47 [I,C]; A61K-0031/55 [I,A]; A61K-0031/55 [I,C]; A61K-0031/655 [I,A]; A61K-0031/655 [I,C]; **A61K-0045/00** [I,A]; **A61K-0045/00** [I,C]; **A61K-0045/06** [I,A]; A61P-0017/00 [I,A]; A61P-0017/00 [I,C]; A61P-0025/00 [I,A]; A61P-0025/00 [I,C]; A61P-0025/16 [I,A]; **A61P-0025/18** [I,A]; A61P-0039/00 [I,C]; A61P-0039/02 [I,A]; A61P-0039/04 [I,A]; A61P-0043/00 [I,A]; A61P-0043/00 [I,C]; C07D-0213/00 [I,C]; C07D-0213/16 [I,A]; C07D-0213/74 [I,A]; C07D-0311/00 [I,C]; C07D-0311/94 [I,A]

AB WO 2001072291 A2 UPAB: 20060118

NOVELTY - Use of a compound which inhibits **metabotropic glutamate** receptor activity, or activation is claimed for the manufacture of a medicament for treatment of movement disorders associated with a poverty of movement.

ACTIVITY - Neuroprotective; antiparkinsonian; neuroleptic; antidote.

MECHANISM OF ACTION - **Metabotropic glutamate** receptor antagonist (preferably **mGlu5** receptor antagonist).

In a reserpine-treated rat model of Parkinson's disease, total mobile counts for animals on a combination therapy ((RS)-1-aminoindane-1,5-dicarboxylic acid (1 mg/kg) together with chloro-APB (0.2 mg/kg) or quinpirole (0.1 mg/kg)) were found to be significantly greater than for animals treated with chloro-APB, quinpirole or vehicle only. This shows that mobility, and therefore the parkinsonian state, was improved in animals given the combination therapy.

USE - The medicament can be used to treat or prevent movement disorders associated with a poverty of movement, including parkinsonism, including idiopathic Parkinson's disease or post-encephalitic parkinsonism, especially parkinsonism resulting from head injury, treatment of schizphrenia, drug intoxication or manganese poisoning, Wilson's disease, progressive supranuclear palsy and some forms of dystonia, (all claimed). Also for treating medical conditions characterized by akinesia, hypokinesia or bradykinesia and conditions characterized by hypertonia.

ADVANTAGE - The **metabotropic glutamate** receptor inhibitors produce fewer side effects than prior art active agents.

MC CPI: B05-B01A; B06-H; B07-D04C; B10-B02E; B14-J01A3; B14-J02B2; B14-J02D3; B14-J05; B14-L06; B14-S03

TECH

PHARMACEUTICALS - Preferred Materials: The active compound is a **metabotropic glutamate** receptor antagonist, especially a selective antagonist. The active compound can be administered in conjunction with an anti-parkinsonian therapy, e.g., gene therapy, cell implantation/transplantation, subthalamic nucleus lesions/deep brain stimulation or Gpi lesions/deep brain stimulation. The anti-parkinsonian therapy especially comprises administration of an anti-parkinsonian agent, e.g., chloro-APB, L-DOPA, apomorphine, ropinirole, pramipexole, cabergoline, bromcriptine, quinpirole, lisuride, pergolide, a dopamine D1 or D2 receptor agonist, a mixed dopamine receptor agonist, an adenosine A2A receptor antagonist, a muscarinic M4 antagonist, a nicotinic agonist, a delta opioid agonist or a NMDA receptor antagonist.

L20 ANSWER 20 OF 21 WPIX COPYRIGHT 2007 THE THOMSON CORP on STN

AN 2001-565550 [63] WPIX

DNC C2001-167877 [63]

TI Use of an antagonist of the **metabotropic glutamate** receptor useful in the manufacture of a medicament for tolerance or dependence therapy

DC B04; D16

IN CONQUET F; CONQUET F I B C M; CORSI M

PA (CONQ-I) CONQUET F; (CORS-I) CORSI M; (GLAX-C) GLAXO GROUP LTD

CYC 93

PI WO--2001066113 A1 20010913 (200163)* EN 41[4] <--

AU---200137634 A 20010917 (200204) EN <--
EP-----1267869 A1 20030102 (200310) EN
JP--2003525902 W 20030902 (200358) JA 47
CN-----1427720 A 20030702 (200361) ZH
US-20030195139 A1 20031016 (200369) EN
NZ------521228 A 20040430 (200431) EN
EP-----1267869 B1 20040519 (200433) EN
DE----60103384 E 20040624 (200442) DE
ES-----2220727 T3 20041216 (200506) ES
DE----60103384 T2 20050616 (200540) DE
AU------783869 B2 20051215 (200654) EN

ADT WO--2001066113 A1 **2001WO-GB0001058 20010309**; AU---200137634 A **2001AU-000037634 20010309**; CN-----1427720 A **2001CN-000808891 20010309**; DE----60103384 E **2001DE-000603384 20010309**; DE----60103384 T2 **2001DE-000603384 20010309**; EP-----1267869 A1 **2001EP-000910051 20010309**; EP-----1267869 B1 **2001EP-000910051 20010309**; DE----60103384 E **2001EP-000910051 20010309**; ES-----2220727 T3 **2001EP-000910051 20010309**; DE----60103384 T2 **2001EP-000910051 20010309**; JP--2003525902 W **2001JP-000564765 20010309**; NZ------521228 A **2001NZ-000521228 20010309**; EP-----1267869 A1 **2001WO-GB0001058 20010309**; JP--2003525902 W **2001WO-GB0001058 20010309**; US-20030195139 A1 **2001WO-GB0001058 20010309**; NZ------521228 A **2001WO-GB0001058 20010309**; EP-----1267869 B1 **2001WO-GB0001058 20010309**; DE----60103384 E **2001WO-GB0001058 20010309**; DE----60103384 T2 **2001WO-GB0001058 20010309**; US-20030195139 A1 2003US-000221128 20030414; AU------783869 B2 **2001AU-000037634 20010309**

FDT DE----60103384 E Based on EP-----1267869 A; ES-----2220727 T3 Based on EP-----1267869 A; DE----60103384 T2 Based on EP-----1267869 A; AU---200137634 A Based on WO--2001066113 A; EP-----1267869 A1 Based on WO--2001066113 A; JP--2003525902 W Based on WO--2001066113 A; NZ------521228 A Based on WO--2001066113 A; EP-----1267869 B1 Based on WO--2001066113 A; DE----60103384 E Based on WO--2001066113 A; DE----60103384 T2 Based on WO--2001066113 A; AU------783869 B2 Based on WO--2001066113 A

PRAI **2000GB-000005700 20000309**

IC ICM A61K-031/44; **A61K-045/00**

IPCI A61K-0031/185 [I,C]; A61K-0031/197 [I,A]; A61K-0031/44 [I,A]; A61K-0031/44 [I,C]; **A61K-0045/00** [I,C]; **A61K-0045/06** [I,A]; A61P-0025/00 [I,C]; A61P-0025/30 [I,A]; A61P-0025/32 [I,A]; A61P-0025/34 [I,A]; A61P-0025/36 [I,A]

IPCR A61K-0031/00 [I,A]; A61K-0031/00 [I,C]; A61K-0031/137 [I,A]; A61K-0031/137 [I,C]; A61K-0031/185 [I,C]; A61K-0031/197 [I,A]; A61K-0031/44 [I,A]; A61K-0031/44 [I,C]; A61K-0031/472 [I,A]; A61K-0031/472 [I,C]; A61K-0031/551 [I,C]; A61K-0031/5513 [I,A]; **A61K-0045/00** [I,A]; **A61K-0045/00** [I,C]; **A61K-0045/06** [I,A]; A61P-0025/00 [I,A]; A61P-0025/00 [I,C]; **A61P-0025/18** [I,A]; A61P-0025/30 [I,A]; A61P-0025/32 [I,A]; A61P-0025/34 [I,A]; A61P-0025/36 [I,A]; G01N-0033/94 [I,A]; G01N-0033/94 [I,C]

AB WO 2001066113 A1 UPAB: 20060117

NOVELTY - Treating a host suffering from tolerance or dependence, comprising administration of an antagonist of a **metabotropic glutamate** receptor 5 (**mGluR5**), is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) products containing the antagonist of **mGluR5** and a therapeutic substance as a combined preparation for simultaneous, separate or sequential use. The use of the substance in the absence of the antagonist could lead to tolerance or dependence of the substance;

(2) use of the **mGluR5** for a method of identifying the product in the treatment of tolerance or dependence, comprising:

(a) contacting a test product with **mGluR5** under condition, that in the absence of the test substance would lead to the activity of the **mGluR5**;

(b) determining if the test product antagonizes the **mGluR5** activity; and

(c) determining if the test product can be used in the treatment of tolerance or dependence;

(3) a pharmaceutical composition comprising the product and a carrier or diluent; and

(4) treating a host suffering from tolerance or dependence involving administering the product to the host.

ACTIVITY - Anti-alcoholic; antismoking; tranquilizer.

MECHANISM OF ACTION - **mGluR5** (**metabotropic glutamate** receptor 5) antagonist.

Nicotine was dissolved in heparinized saline (0.09 % NaCl, 0.5 UI/ml heparin) and the pH was adjusted to 7.4 with NaOH. After acquisition of the operant behavior, rats were maintained on a daily schedule of nicotine self-administration for at least 2-3 weeks. On test day, 24 hours after the last nicotine self-administration session, rats were exposed to a multiple relapse schedule consisting of two components. Firstly a 30-minute phase with exposure to the context and continuously upon responding to conditioned stimuli (tone plus cue lamp) previously paired to nicotine self-administration. Then a non-contingent subcutaneous injection of nicotine (0.15 mg/kg) was delivered to rats as priming and nicotine-paired lever presses were measured during the second 120-minute phase. 2-Methyl-6-(phenylethynyl)-pyridine (A) was dissolved in saline (0.09 % NaCl) and was given to rats at the doses of 1, 10 mg/kg or vehicle intravenously, single bolus in a volume of 1 ml/kg, 5 minutes prior to the start of the relapse test session days. At least two stable self-administration sessions elapsed between the different relapse test sessions. A-induced inhibition of reinstatement of responding for nicotine-paired lever at both doses 1 and 10 mg/kg (respectively -60 % and -86% compared to responding after vehicle treatment) during the cue component. Both doses were also effective to reduce reinstatement during the nicotine component phase at all the time-points, with a maximal effect measured at the 90th minute: respectively -42 % and -98 % compared to the responding after vehicle treatment.

USE - In the manufacture of a medicament for used in a method of tolerance or dependence therapy such as in the treatment of smoking dependence, in the treatment of substance, preferably nicotine, cocaine, or a therapeutic substance such as amphetamine, or related drugs e.g. benzodiazepene, opiate or ethanol) withdrawal or cessation, bulimia nervosa, anorexia nervosa, gambling dependence, sex dependence or obsessive compulsive disorders. It can also be used for identifying a product for use in the treatment of tolerance or dependence. (Claimed).

ADVANTAGE - The compound is a selective antagonist of the **mGluR5**, diminishes or abolishes the effect of a ligand (agonist) which typically activates **mGluR5**, and can reduce the reinstatement of nicotine-seeking behavior.

MC CPI: B07-D04C; B10-B04B; B14-E11; B14-E12; B14-J01B4; B14-M01A; B14-M01B; B14-M01C; D05-H09

L20 ANSWER 21 OF 21 WPIX COPYRIGHT 2007 THE THOMSON CORP on STN
AN 2000-303626 [26] WPIX
DNC C2000-092157 [26]
TI Use of **metabotropic glutamate** receptor 5 antagonists for the treatment of pain particularly inflammatory pain and associated hyperalgesia, neuropathic pain or chronic pain and in the treatment of anxiety is new
DC B03
IN ALLGEIER H; COSFORD N D; FLOR P J; GASPARINI F; GENTSCH C; HESS S D; JOHNSON E C; KUHN R; TRICKLEBANK M; URBAN L; VARNEY M A; VELI ELEBI G; VELICELEBI G; WALKER K; ALLGERIER H
PA (ALLG-I) ALLGEIER H; (COSF-I) COSFORD N D; (FLOR-I) FLOR P J; (GASP-I) GASPARINI F; (GENT-I) GENTSCH C; (HESS-I) HESS S D; (JOHN-I) JOHNSON E C; (KUHN-I) KUHN R; (NOVS-C) NOVARTIS AG; (NOVS-C) NOVARTIS PHARMA GMBH; (NOVS-C) NOVARTIS-ERFINDUNGEN VERW GES MBH; (SIBI-N) SIBIA NEUROSCIENCES INC; (TRIC-I) TRICKLEBANK M; (URBA-I) URBAN L; (VARN-I) VARNEY M A; (VELI-I) VELICELEBI G; (WALK-I) WALKER K
CYC 88
PI WO--2000020001 A1 20000413 (200026)* EN 20[0] <--

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     AU-----9961984  A  20000426 (200036)  EN                                <--
     NO---200101440  A  20010515 (200137)  NO                                <--
     BR-----9914215  A  20010703 (200141)  PT                                <--
     EP-----1117403  A1 20010725 (200143)  EN                                <--
     SK---200100438  A3 20010806 (200157)  SK                                <--
     US-20010056084  A1 20011227 (200206)  EN                                <--
     CN-----1321087  A  20011107 (200216)  ZH                                <--
     KR--2001088832  A  20010928 (200220)  KO                                <--
     HU---200200553  A2 20020729 (200258)  HU                                <--
     JP--2002526408  W  20020820 (200258)  JA  25                            <--
     ZA---200102637  A  20021030 (200282)  EN  34                            <--
     AU------765644  B  20030925 (200373)  EN
     NZ------510743  A  20031031 (200380)  EN
     EP-----1117403  B1 20031210 (200405)  EN
     DE----69913548  E  20040122 (200415)  DE
     ES-----2213389  T3 20040816 (200455)  ES
     RU-----2232017  C2 20040710 (200455)  RU
     CN-----1187048  C  20050202 (200622)  ZH
     PH--1199902452  B1 20050324 (200665)  EN
ADT  WO--2000020001 A1 1999WO-EP0007239  19990930; AU-----9961984 A
     1999AU-000061984  19990930; AU------765644 B 1999AU-000061984
     19990930; BR-----9914215 A 1999BR-000014215  19990930;
     CN-----1321087 A 1999CN-000811711  19990930; CN-----1187048 C
     1999CN-000811711  19990930; DE----69913548 E 1999DE-000613548
     19990930; EP-----1117403 A1 1999EP-000948905  19990930;
     EP-----1117403 B1 1999EP-000948905  19990930; DE----69913548 E
     1999EP-000948905  19990930; ES-----2213389 T3
     1999EP-000948905  19990930; NZ------510743 A 1999NZ-000510743
     19990930; NO---200101440 A 1999WO-EP0007239  19990930;
     BR-----9914215 A 1999WO-EP0007239  19990930; EP-----1117403 A1
     1999WO-EP0007239  19990930; SK---200100438 A3
     1999WO-EP0007239  19990930; US-20010056084 A1 Cont of
     1999WO-EP0007239  19990930; JP--2002526408 W 1999WO-EP0007239
     19990930; HU---200200553 A2 1999WO-EP0007239  19990930;
     NZ------510743 A 1999WO-EP0007239  19990930; EP-----1117403 B1
     1999WO-EP0007239  19990930; DE----69913548 E 1999WO-EP0007239
     19990930; RU-----2232017 C2 1999WO-EP0007239  19990930;
     JP--2002526408 W 2000JP-000573360  19990930; RU-----2232017 C2
     2001RU-000111868  19990930; SK---200100438 A3
     2001SK-000000438  19990930; NO---200101440 A 2001NO-000001440
     20010321; US-20010056084 A1 2001US-000821416  20010329;
     ZA---200102637 A 2001ZA-000002637  20010330; KR--2001088832 A
     2001KR-000704152  20010331; HU---200200553 A2
     2002HU-000000553  19990930; PH--1199902452 B1
     1999PH-000002452  19990930
FDT  AU------765644 B Previous Publ AU-----9961984 A; DE----69913548 E Based on
     EP-----1117403 A; ES-----2213389 T3 Based on EP-----1117403 A;
     AU-----9961984 A Based on WO--2000020001 A; BR-----9914215 A Based on
     WO--2000020001 A; EP-----1117403 A1 Based on WO--2000020001 A;
     SK---200100438 A3 Based on WO--2000020001 A; JP--2002526408 W Based on
     WO--2000020001 A; HU---200200553 A2 Based on WO--2000020001 A;
     AU------765644 B Based on WO--2000020001 A; NZ------510743 A Based on
     WO--2000020001 A; EP-----1117403 B1 Based on WO--2000020001 A;
     DE----69913548 E Based on WO--2000020001 A; RU-----2232017 C2 Based on
     WO--2000020001 A
PRAI 1998US-000220813  19981223
       1998GB-000021503  19981002
IC   ICM A61K-8GB/; A61K-031/44; A61K-045/00
IPCR A61K-0031/44 [I,A]; A61K-0031/44 [I,C]; A61K-0031/4402 [I,A];
     A61K-0031/4402 [I,C]; A61K-0031/4418 [I,A]; A61K-0031/4418 [I,C];
     A61K-0045/00 [I,A]; A61K-0045/00 [I,C]; A61P-0025/00
     [I,C]; A61P-0025/04 [I,A]; A61P-0025/18 [I,A]; A61P-0025/24
     [I,A]; A61P-0029/00 [I,A]; A61P-0029/00 [I,C]; A61P-0043/00 [I,A];
     A61P-0043/00 [I,C]; C07D-0213/00 [I,C]; C07D-0213/06 [I,A]; C07D-0213/16
     [I,A]; C07D-0213/26 [I,A]; C07D-0213/65 [I,A]
AB   WO 2000020001 A1   UPAB: 20060331
```

NOVELTY - Use of **metabotropic glutamate** receptor 5 (**mGluR5**) antagonists (I) for the treatment of pain and anxiety is new.

ACTIVITY - Analgesic; tranquilizer.

In a mouse partial sciatic nerve ligation model of neuropathic pain using a modification of the method of Seltzer et al. (Pain, 43, 205-218, 1990), intraplantar administration of specific **metabotropic glutamate** receptor-5 antagonists produced a significant reversal of mechanical hyperalgesia at 1-100 mg/kg.

MECHANISM OF ACTION - Peripheral **metabotropic glutamate** receptor antagonist.

USE - (I) is used in the treatment of pain particularly inflammatory pain and associated hyperalgesia, neuropathic pain or chronic pain and in the treatment of anxiety.

ADVANTAGE - (I) is a specific **metabotropic glutamate** receptor 5 antagonist with an affinity of 100-400 times greater than to the **metabotropic glutamate** receptor 1. (I) does not penetrate the central nervous system or cross the blood-brain barrier (claimed). (I) has no toxicological effects or mutagenic potential.

MC CPI: B07-D04C; B14-C01; B14-J01B4; B14-L06

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FILE LAST UPDATED: 3 Jun 2007 (20070603/ED)

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L60 ANSWER 1 OF 14 HCAPLUS COPYRIGHT 2007 ACS on STN
AN **2006:809360** HCAPLUS
DN 145:202709
TI Subchronic administration of LY354740 does not modify ketamine-evoked behavior and neuronal activity in rats
AU Imre, Gabor; Fokkema, Dirk S.; Ter Horst, Gert J.
CS Department of Psychiatry, University Medical Center Groningen, University of Groningen, Groningen, 9700 RB, Neth.
SO European Journal of Pharmacology (2006), 544(1-3), 77-81
CODEN: EJPHAZ; ISSN: 0014-2999
PB Elsevier B.V.
DT Journal
LA English
AB Acute treatment with LY354740 {1S,2S,5R,6S-2-aminobicyclo[3.1.0]hexane-2,6-dicarboxylate monohydrate}, a potent and selective agonist for group II metabotropic glutamate receptors (mGlu2/3), has previously been shown to

block some schizophrenia-like effects of N-methyl-D-aspartate (NMDA) receptor antagonists, suggesting a novel therapeutic strategy for schizophrenia. The present study examined the effects of subchronic pretreatment with LY354740 (0.3, 3 and 10 mg/kg i.p.) on ketamine-evoked (12 mg/kg s.c.) prepulse inhibition deficits, hyperlocomotion and c-fos expression. At all doses, LY354740 failed to reverse both behavioral and neuronal effects of the ketamine. These results therefore do not support the putative antipsychotic role of LY354740.

CC 1-11 (Pharmacology)

IT **Glutamate receptors**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(metabotropic, **group II**, agonist; subchronic administration of LY354740 does not modify ketamine-evoked behavior and neuronal activity in rats)

IT **Glutamate receptors**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(metabotropic, **group III**, agonist; subchronic administration of LY354740 does not modify ketamine-evoked behavior and neuronal activity in rats)

IT **Antipsychotics**
Cognitive disorders
Hyperkinesia
Schizophrenia
(subchronic administration of LY354740 does not modify ketamine-evoked behavior and neuronal activity in rats)

RE.CNT 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L60 ANSWER 2 OF 14 HCAPLUS COPYRIGHT 2007 ACS on STN
AN **2005:984332** HCAPLUS
DN 143:278220
TI Agonists and antagonists for group III metabotropic glutamate receptors 6, 7 and 8
AU Yang, Zhi-Qiang
CS Department of Medicinal Chemistry, Merck Research Laboratories, Merck and Co., West Point, PA, 19486, USA
SO Current Topics in Medicinal Chemistry (Sharjah, United Arab Emirates) (2005), 5(9), 913-918
CODEN: CTMCCL; ISSN: 1568-0266
PB Bentham Science Publishers Ltd.
DT Journal; General Review
LA English
AB A review. Metabotropic glutamate receptors (mGluRs) have been implicated in a variety of neurol. and psychiatric disorders. This article describes recent progress in the development of agonists and antagonists for mGluR 6, 7, and 8. All of them are conformationally constrained or substituted amino acids, and they act at N-terminal extracellular glutamate binding site. These ligands serve as valuable tools for studying physiol. and pathol. roles of mGluRs. However, their therapeutic potential may be restricted by their poor CNS penetration and lack of selectivity for individual receptors.

CC 1-0 (Pharmacology)

IT **Antipsychotics**
Conformation
Mental and behavioral disorders
Structure-activity relationship
(agonists and antagonists for group III metabotropic glutamate receptors 6, 7 and 8)

IT **Glutamate receptors**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(metabotropic, **group III**; agonists and antagonists for **group III** metabotropic glutamate receptors 6, 7 and 8)

IT **Glutamate receptors**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(metabotropic, mGluR6; agonists and antagonists for **group**

III metabotropic glutamate receptors 6, 7 and 8)
IT **Glutamate receptors**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(metabotropic, mGluR7; agonists and antagonists for **group**
III metabotropic glutamate receptors 6, 7 and 8)
IT **Glutamate receptors**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(metabotropic, mGluR8; agonists and antagonists for **group**
III metabotropic glutamate receptors 6, 7 and 8)
RE.CNT 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L60 ANSWER 3 OF 14 HCAPLUS COPYRIGHT 2007 ACS on STN
AN **2004:448726** HCAPLUS
DN 141:116997
TI NAAG peptidase inhibition reduces locomotor activity and some stereotypes in the PCP model of schizophrenia via group II mGluR
AU Olszewski, Rafal T.; Bukhari, Noreen; Zhou, Jia; Kozikowski, Alan P.; Wroblewski, Jarda T.; Shamimi-Noori, Susan; Wroblewska, Barbara; Bzdega, Tomasz; Vicini, Stefano; Barton, Franca B.; Neale, Joseph H.
CS Department of Biology, Georgetown University, Washington, DC, USA
SO Journal of Neurochemistry (2004), 89(4), 876-885
CODEN: JONRA9; ISSN: 0022-3042
PB Blackwell Publishing Ltd.
DT Journal
LA English
AB Phencyclidine (PCP) administration elicits pos. and neg. symptoms that resemble those of schizophrenia and is widely accepted as a model for the study of this human disorder. Group II metabotropic glutamate receptor (mGluR) agonists have been reported to reduce the behavioral and neurochem. effects of PCP. The peptide neurotransmitter, N-acetylaspartylglutamate (NAAG), is a selective group II agonist. The authors synthesized and characterized a urea-based NAAG analog, ZJ43. This novel compound is a potent inhibitor of enzymes, glutamate carboxypeptidase II (Ki = 0.8 nM) and III (Ki = 23 nM) that deactivate NAAG following synaptic release. ZJ43 (100 μM) does not directly interact with NMDA receptors or metabotropic glutamate receptors. Administration of ZJ43 significantly reduced PCP-induced motor activation, falling while walking, stereotypic circling behavior, and head movements. To test the hypothesis that this effect of ZJ43 was mediated by increasing the activation of mGluR3 via increased levels of extracellular NAAG, the group II mGluR selective antagonist LY341495 was co-administered with ZJ43 prior to PCP treatment. This antagonist completely reversed the effects of ZJ43. Addnl., LY341495 alone increased PCP-induced motor activity and head movements suggesting that normal levels of NAAG act to moderate the effect of PCP on motor activation via a group II mGluR. These data support the view that NAAG peptidase inhibitors may represent a new therapeutic approach to some of the components of schizophrenia that are modeled by PCP.
CC 1-11 (Pharmacology)
Section cross-reference(s): 34
IT **Antipsychotics**
Disease models
Human
Schizophrenia
(NAAG peptidase inhibition reduces locomotor activity and some stereotypes in PCP model of schizophrenia via group II mGluR)
IT **Glutamate receptors**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(metabotropic, **group II**; NAAG peptidase inhibition reduces locomotor activity and some stereotypes in PCP model of schizophrenia via **group II** mGluR)
RE.CNT 50 THERE ARE 50 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L60 ANSWER 4 OF 14 HCAPLUS COPYRIGHT 2007 ACS on STN

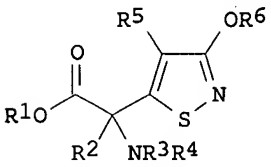
AN **2003:926296** HCAPLUS
DN 140:139339
TI Stimulation of α1-adrenoceptors in the rat medial prefrontal cortex increases the local in vivo 5-hydroxytryptamine release: Reversal by antipsychotic drugs
AU Amargos-bosch, Merce; Adell, Albert; Bortolozzi, Analia; Artigas, Francesc
CS Department of Neurochemistry, IDIBAPS, Institut d' Investigacions Biomediques de Barcelona (CSIC), IDIBAPS, Barcelona, Spain
SO Journal of Neurochemistry (2003), 87(4), 831-842
CODEN: JONRA9; ISSN: 0022-3042
PB Blackwell Publishing Ltd.
DT Journal
LA English
AB Pyramidal neurons of the medial prefrontal cortex (mPFC) project to midbrain serotonergic neurons and control their activity. The stimulation of prefrontal 5-HT2A and AMPA receptors increases pyramidal and serotonergic cell firing, and 5-hydroxytryptamine (5-HT) release in mPFC. As the mPFC contains abundant α1-adrenoceptors whose activation increases the excitability of pyramidal neurons, we examined the effects of their stimulation on local 5-HT release, using microdialysis. The application of the α1-adrenoceptor agonist cirazoline by reverse dialysis increased the prefrontal 5-HT release in a concentration-dependent manner, an effect antagonized by coperfusion of TTX, prazosin (α1-adrenoceptor antagonist), BAY + 3702 (5-HT1A agonist), NBQX (AMPA/KA antagonist) and 1S,3S-ACPD (mGluR II/III agonist), but not by MK-801 (NMDA antagonist). Cirazoline also enhanced the increase in 5-HT release induced by DOI (5-HT2A/2C agonist) and AMPA. In addition, M100907 (5-HT2A antagonist) but not SB-242084 (5-HT2C antagonist) reversed the cirazoline- and AMPA-induced 5-HT release. These results suggest that the stimulation of prefrontal α1-adrenoceptors activates pyramidal afferents to ascending serotonergic neurons. The effect of cirazoline was also reversed by coperfusion of classical (chlorpromazine, haloperidol) and atypical (clozapine, **olanzapine**) antipsychotics, which suggests that a functional antagonism of the α1-adrenoceptor-mediated activation of prefrontal neurons may partly underlie their therapeutic action.
CC 1-11 (Pharmacology)
IT **Glutamate receptors**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(metabotropic, **group II**; α1-adrenoceptor stimulation in medial prefrontal cortex increases local 5-hydroxytryptamine release and is reversed by antipsychotics)
IT **Antipsychotics**
α1-Adrenoceptor agonists
(α1-adrenoceptor stimulation in medial prefrontal cortex increases local 5-hydroxytryptamine release and is reversed by antipsychotics)
IT 50-53-3, Chlorpromazine, biological studies 52-86-8, Haloperidol 5786-21-0, Clozapine **132539-06-1**, **Olanzapine**
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); BIOL (Biological study)
(α1-adrenoceptor stimulation in medial prefrontal cortex increases local 5-hydroxytryptamine release and is reversed by antipsychotics)
RE.CNT 91 THERE ARE 91 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L60 ANSWER 5 OF 14 HCAPLUS COPYRIGHT 2007 ACS on STN
AN **2003:678795** HCAPLUS
DN 139:214240
TI Preparation of thioibotenic acid and derivatives thereof as agonists at the metabotropic glutamic acid Group II and III receptors
IN Bunch, Lennart; Madsen, Ulf; Braeuner-Osborne, Hans; Krogsgaard-Larsen, Povl; Grube Jorgensen, Charlotte
PA H. Lundbeck A/S, Den.
SO PCT Int. Appl., 20 pp.

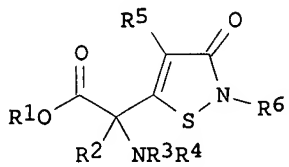
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO2003070712	A1	20030828	2003WO-DK00104	20030217 <--
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU2003205558	A1	20030909	2003AU-0205558	20030217 <--
PRAI 2002DK-0000258	A	20020219 <--		
2002US-358335P	P	20020219 <--		
2003WO-DK00104	W	20030217		

OS MARPAT 139:214240
GI



I



II

AB The title compds. [I or II; R1 = H, alkyl, cycloalkyl, etc.; R2 = H, alkyl, aryl, etc.; R3, R4 = H, alkyl, cycloalkyl, etc.; R5 = H, halo, CN, etc.; or R2 and R5 together = CR7:CR8 or CR7R7aCR8R8a (wherein R7, R7a, R8, R8a = H, alkyl, cycloalkyl, etc.); R6 = H, alkyl, aryl, etc.] which are agonists at the metabotropic glutamic acid Group II and III receptors, were prepared and formulated. E.g., a 4-step synthesis of the thioibotenic acid II [R1-R6 = H] (starting from 3-hydroxyisothiazole) which has a reduced agonist effect at the NMDA receptor as compared to ibotenic acid and an increased agonist effect at mGluR2 relative to ibotenic acid as well as agonist activity in the μM range at mGluR4, was given.

IC ICM C07D-275/03
ICS C07D-275/04; A61K-031/425
CC 26-9 (Biomolecules and Their Synthetic Analogs)
Section cross-reference(s): 1, 34, 63
IT **Glutamate receptors**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(metabotropic, mGluR2; preparation of thioibotenic acid and its derivs. as agonists at the metabotropic glutamic acid **Group II** and III receptors)
IT **Glutamate receptors**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(metabotropic, mGluR4; preparation of thioibotenic acid and its derivs. as agonists at the metabotropic glutamic acid **Group II** and III receptors)
IT Analgesics
Anti-Alzheimer's agents
Anticonvulsants
Antiparkinsonian agents
Antipsychotics
Anxiolytics
(preparation of thioibotenic acid and its derivs. as agonists at the metabotropic glutamic acid Group II and III receptors)

IT Alzheimer's disease
Anxiety
Epilepsy
Pain
Parkinson's disease
Schizophrenia
(treatment of; preparation of thioibotenic acid and its derivs. as agonists at the metabotropic glutamic acid Group II and III receptors)
RE.CNT 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L60 ANSWER 6 OF 14 HCAPLUS COPYRIGHT 2007 ACS on STN
AN **2003:653128** HCAPLUS
DN 140:53795
TI Group II mGlu receptor activation suppresses norepinephrine release in the ventral hippocampus and locomotor responses to acute ketamine challenge
AU Lorrain, Daniel S.; Schaffhauser, Herve; Campbell, Una C.; Baccei, Christopher S.; Correa, Lucia D.; Rowe, Blake; Rodriguez, Dana E.; Anderson, Jeffery J.; Varney, Mark A.; Pinkerton, Anthony B.; Vernier, Jean-Michel; Bristow, Linda J.
CS Department of Neuropharmacology, Merck Research Laboratories, San Diego, CA, USA
SO Neuropsychopharmacology (2003), 28(9), 1622-1632
CODEN: NEROEW; ISSN: 0893-133X
PB Nature Publishing Group
DT Journal
LA English
AB Group II mGlu receptor agonists (eg LY379268 and LY354740) have been shown to reverse many of the behavioral responses to PCP as well as glutamate release elicited by PCP and ketamine. In the present set of expts., the authors used in vivo microdialysis to show that, in addition to reversing PCP- and ketamine-evoked glutamate release, group II mGlu receptor stimulation also prevents ketamine-evoked norepinephrine (NE) release. Pretreating animals with the mixed 2/3 metabotropic glutamate (mGlu2/3) receptor agonist LY379268 (0.3-10 mg/kg) dose-dependently inhibited ketamine (25 mg/kg)-evoked NE release in the ventral hippocampus (VHipp). Ketamine hyperactivity was also reduced in a similar dose range. Following the authors' initial observation on NE release, they conducted a series of microinjection expts. to reveal that the inhibitory effects of LY379268 on VHipp NE release may be linked to glutamate transmission within the medial prefrontal cortex. Finally, the authors were able to mimic the inhibitory effects of LY379268 on ketamine-evoked NE release by using a novel mGlu2 receptor selective pos. modulator. (+/-) 2,2,2-Trifluoroethyl [3-(1-methyl-butoxy)-phenyl]-pyridin-3-ylmethyl-sulfonamide (2,2,2-TEMPS, characterized through in vitro GTPγS binding) at a dose of 100 mg/kg significantly reduced the NE response. Together, these results demonstrate a novel means to suppress noradrenergic neurotransmission (i.e. by activating mGlu2 receptors) and may, therefore, have important implications for neuropsychiatric disorders in which aberrant activation of the noradrenergic system is thought to be involved.
CC 2-8 (Mammalian Hormones)
Section cross-reference(s): 1, 14
IT **Antipsychotics**
Human
Schizophrenia
(group II mGlu receptor activation suppression of norepinephrine release in ventral hippocampus and locomotor responses to acute ketamine challenge in schizophrenia model)
IT **Glutamate receptors**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(metabotropic, **group II**; **group II**
mGlu receptor activation suppression of norepinephrine release in ventral hippocampus and locomotor responses to acute ketamine challenge in schizophrenia model)
IT **Glutamate receptors**

RL: BSU (Biological study, unclassified); BIOL (Biological study)
(metabotropic, mGluR2; **group II** mGlu receptor
activation suppression of norepinephrine release in ventral hippocampus and locomotor responses to acute ketamine challenge in schizophrenia model)
RE.CNT 51 THERE ARE 51 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L60 ANSWER 7 OF 14 HCAPLUS COPYRIGHT 2007 ACS on STN
AN **2003:567563** HCAPLUS
DN 140:12895
TI Antipsychotic action of selective group II metabotropic glutamate receptor agonist MGS0008 and MGS0028 on conditioned avoidance responses in the rat
AU Takamori, Kazuaki; Hirota, Shiho; Chaki, Shigeyuki; Tanaka, Makoto
CS Research Management Section, Medicinal Research Laboratories, Taisho Pharmaceutical Co. Ltd., Saitama, 330-8530, Japan
SO Life Sciences (2003), 73(13), 1721-1728
CODEN: LIFSAK; ISSN: 0024-3205
PB Elsevier Science Inc.
DT Journal
LA English
AB The present study was designed to investigate the antipsychotic-like effects of selective group II metabotropic glutamate receptor (mGluR) agonists, 5-{2-[4-(6-fluoro-1H-indole-3-yl) piperidin-1-yl]ethyl}-4-(4-fluorophenyl)thiazole-2-carboxylic acid amide (MGS0008) and (1R, 2S, 5S, 6S)-2-amino-6-fluoro-4-oxobicyclo[3.1.0]hexane-2,6-dicarboxylic acid monohydrate (MGS0028) on conditioned avoidance responses in rats. MGS0008 (1, 3 and 10 mg/kg, p.o.) and MGS0028 (0.3, 1 and 3 mg/kg, p.o.) significantly and reduced conditioned avoidance responses in a dose-dependent fashion. Similar effects were seen with LY418426 (0.3, 1 and 3 mg/kg, p.o.), but not with LY354740 (3, 10 and 30 mg/kg, p.o.), both of which are selective agonists for group II mGluR. Since this effect is seen with a wide range of antipsychotics, such as haloperidol and clozapine [Life Sciences 71 (2002) 947], group II mGluR agonists deserve further attention for possible antipsychotic activity.
CC 1-11 (Pharmacology)
IT **Antipsychotics**
(antipsychotic action of selective group II metabotropic glutamate receptor agonist on conditioned avoidance responses)
IT **Glutamate receptors**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(metabotropic, **group II**; antipsychotic action of selective **group II** metabotropic glutamate receptor agonist on conditioned avoidance responses)
RE.CNT 38 THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L60 ANSWER 8 OF 14 HCAPLUS COPYRIGHT 2007 ACS on STN
AN **2002:512129** HCAPLUS
DN 137:345962
TI Group II mGlu receptor agonists inhibit behavioural and electrophysiological effects of DOI in mice
AU Klodzinska, Aleksandra; Bijak, Maria; Tokarski, Krzysztof; Pilc, Andrzej
CS Polish Academy of Sciences, Institute of Pharmacology, Krakow, 31-343, Pol.
SO Pharmacology, Biochemistry and Behavior (**2002**), 73(2), 327-332
CODEN: PBBHAU; ISSN: 0091-3057
PB Elsevier Science Inc.
DT Journal
LA English
AB It has been suggested that metabotropic glutamate (mGlu) receptor agonists selective for Group II mGlu receptors may have antipsychotic action. Therefore, we studied whether the effects, which could be related to psychotomimetic action of hallucinogenic drugs, are inhibited by Group II mGlu receptor agonists. The selective mGlu2/3 agonists LY 354740 and LY 379268 inhibited (±)1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane

(DOI)-induced head twitches in mice in a dose-dependent manner. Furthermore, LY 379268 suppressed an increase in the frequency of spontaneous excitatory synaptic potentials induced by bath-applied DOI in layer V pyramidal cells recorded in the murine medial frontal cortex. The data indicate that Group II mGlu receptor agonists may counteract the effects of hallucinogenic drugs.

CC 1-11 (Pharmacology)
Section cross-reference(s): 2

IT **Antipsychotics**
Neurotransmission
(group II metabotropic glutamate receptor agonists inhibit behavioral and brain electrophysiol. effects of DOI in mice)

IT **Glutamate receptors**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(metabotropic; **group II** metabotropic glutamate receptor agonists inhibit behavioral and brain electrophysiol. effects of DOI in mice)

RE.CNT 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L60 ANSWER 9 OF 14 HCAPLUS COPYRIGHT 2007 ACS on STN
AN **2002:200470** HCAPLUS
DN 137:123431
TI Comparative analysis of group II metabotropic glutamate receptor immunoreactivity in Brodmann's area 46 of the dorsolateral prefrontal cortex from patients with schizophrenia and normal subjects
AU Crook, J. M.; Akil, M.; Law, B. C. W.; Hyde, T. M.; Kleinman, J. E.
CS Section on Neuropathology, Clinical Brain Disorders Branch, National Institute of Mental Health, Bethesda, MD, 20892, USA
SO Molecular Psychiatry (**2002**), 7(2), 157-164
CODEN: MOPSFQ; ISSN: 1359-4184
PB Nature Publishing Group
DT Journal
LA English
AB Glutamate is the primary excitatory neurotransmitter in the mammalian central nervous system, and a key neurotransmitter in prefrontal cortical function. Converging lines of evidence implicate prefrontal cortical dysfunction in the neurobiol. of schizophrenia. Thus, aberrant glutamate neurotransmission may underlie schizophrenia and other complex disorders of behavior. Group II metabotropic receptors (mGluRs) are important modulators of glutamatergic and non-glutamatergic neurotransmission. Moreover, in an animal model, an agonist for group II mGluRs has been shown to reverse the behavioral, locomotor, and cognitive effects of the psychotomimetic drug phencyclidine. Accordingly, group II mGluRs constitute attractive targets for the pharmacotherapeutics and study of schizophrenia. Using immunocytochem. and Western Immunoblotting, the authors compared the localization and levels of group II mGluRs in Brodmann's area 46 of the dorsolateral prefrontal cortex from patients with schizophrenia and normal subjects. Consistent with previous reports, the authors found that immunolabeling of group II mGluRs is prominent in Brodmann's area 46. The majority of labeling was present on axon terminals distributed in a lamina-specific fashion. No apparent difference in the cellular localization or laminar distribution of immunoreactive group II mGluRs was noted between the two diagnostic groups. Similarly, the levels of receptor immunoreactivity determined by quant. Western Immunoblotting were comparable between schizophrenic patients and normal subjects. The authors conclude that while the function of group II mGluRs in Brodmann's area 46 of dorsolateral prefrontal cortex may be altered in patients with schizophrenia, this is not evident at the level of protein expression using an antibody against mGluR2 and mGluR3.

CC 14-10 (Mammalian Pathological Biochemistry)
Section cross-reference(s): 2

IT Axon
Human
Schizophrenia

(group II metabotropic glutamate receptor localization and levels in Brodmann's area 46 of dorsolateral prefrontal cortex in schizophrenia)

IT **Glutamate receptors**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(metabotropic, mGluR2, mglur2; **group II** metabotropic glutamate receptor localization and levels in Brodmann's area 46 of dorsolateral prefrontal cortex in schizophrenia)

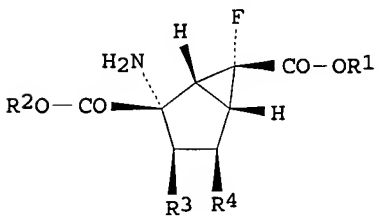
IT **Glutamate receptors**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(metabotropic, mGluR3, mglur3; **group II** metabotropic glutamate receptor localization and levels in Brodmann's area 46 of dorsolateral prefrontal cortex in schizophrenia)

RE.CNT 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L60 ANSWER 10 OF 14 HCAPLUS COPYRIGHT 2007 ACS on STN
AN **2002:10425** HCAPLUS
DN 136:85627
TI Preparation of bicyclo[3.1.0]dicarboxylic acid derivatives as group 2 metabotropic glutamate receptor agonists
IN Nakazato, Atsuro; Kumagai, Toshihito; Kanuma, Kosuke; Sakagami, Kazunari
PA Taisho Pharmaceutical Co., Ltd., Japan
SO PCT Int. Appl., 25 pp.
CODEN: PIXXD2
DT Patent
LA Japanese
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO2002000605	A1	20020103	2001WO-JP05550	20010628 <--
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU2001067854	A5	20020108	2001AU-0067854	20010628 <--
CA---2411059	A1	20021206	2001CA-2411059	20010628 <--
EP---1295865	A1	20030326	2001EP-0945657	20010628 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
US2003134902	A1	20030717	2002US-0297479	20021206 <--
US---6770676	B2	20040803		
HK---1056868	A1	20051202	2003HK-0109245	20031219 <--
PRAI 2000JP-0195239	A	20000628 <--		
2001WO-JP05550	W	20010628 <--		

OS MARPAT 136:85627
GI



I

AB 2-Amino-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid derivs. represented by the general formula I [R1, R2 = H, alkyl, etc.; when R3 is OH, R4 is H; or R3R4 = bond] are prepared These compds. are useful as drugs, in particular, group 2 metabotropic glutamate receptor agonists having therapeutic and preventive effects on, for example, psychiatric diseases such as schizophrenia, anxiety, etc. (1R,2R,3R,5R,6R)-2-Amino-6-fluoro-3-hydroxybicyclo[3.1.0]hexane-2,6-dicarboxylic acid was prepared and its bioactivity was demonstrated.
IC ICM C07C-229/50
ICS A61K-031/198; A61K-031/223; A61P-009/10; A61P-025/08; A61P-025/16; A61P-025/18; A61P-025/22; A61P-043/00
CC 24-4 (Alicyclic Compounds)
Section cross-reference(s): 1
IT **Glutamate receptors**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(metabotropic; preparation of bicyclo[3.1.0]dicarboxylic acid derivs. as **group 2** metabotropic glutamate receptor agonists)
IT Alzheimer's disease
Cognitive disorders
Drug dependence
Head and Neck, disease
Movement disorders
Parkinson's disease
Schizophrenia
(preparation and therapeutic effect of bicyclo[3.1.0]dicarboxylic acid derivs. as group 2 metabotropic glutamate receptor agonists)
RE.CNT 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

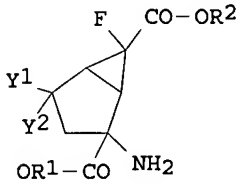
L60 ANSWER 11 OF 14 HCAPLUS COPYRIGHT 2007 ACS on STN
AN **2001:456987** HCAPLUS
DN 135:297863
TI Discovery of group II mGluR receptor agonists
AU Okuyama, Shigeru
CS Department of Medical Project, Taisho Pharmaceutical Co., Ltd., Japan
SO Oyo Yakuri **(2001)**, 60(4), 115-117
CODEN: OYYAA2; ISSN: 0300-8533
PB Oyo Yakuri Kenkyukai
DT Journal; General Review
LA Japanese
AB A review, with 11 refs., of the discovery of group II mGluR receptor agonists, including MGS 0008 and MGS0028, for treatment of schizophrenia.
CC 1-0 (Pharmacology)
IT **Schizophrenia**
(discovery of group II mGluR receptor agonists for treatment of schizophrenia)
IT **Glutamate receptors**
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(metabotropic; discovery of **group II** mGluR receptor agonists for treatment of schizophrenia)

L60 ANSWER 12 OF 14 HCAPLUS COPYRIGHT 2007 ACS on STN
AN **2000:161245** HCAPLUS
DN 132:208130
TI Preparation of aminofluorobicyclohexanedicarboxylic acid derivatives as group-2 metabotropic glutamate receptor agonists
IN Nakazato, Atsuro; Kumagai, Toshihito; Sakagami, Kazunari; Tomisawa, Kazuyuki
PA Taisho Pharmaceutical Co., Ltd., Japan
SO PCT Int. Appl., 47 pp.
CODEN: PIXXD2
DT Patent
LA Japanese
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO2000012464	A1	20000309	1999WO-JP03984	19990726 <--
	W: AU, CA, CN, KR, US				
	RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	CA---2341865	A1	20000309	1999CA-2341865	19990726 <--
	CA---2341865	C	20060117		
	AU---9948007	A1	20000321	1999AU-0048007	19990726 <--
	AU----746806	B2	20020502		
	JP2000336071	A	20001205	1999JP-0211398	19990726 <--
	EP---1110943	A1	20010627	1999EP-0931532	19990726 <--
	EP---1110943	B1	20040616		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
	AT----269293	T	20040715	1999AT-0931532	19990726 <--
	PT---1110943	T	20040831	1999PT-0931532	19990726 <--
	ES---2222715	T3	20050201	1999ES-0931532	19990726 <--
	US---6333428	B1	20011225	2001US-0763408	20010222 <--
	HK---1049996	A1	20060915	2003HK-0102289	20030331 <--
PRAI	1998JP-0246343	A	19980831	<--	
	1999JP-0082607	A	19990325	<--	
	1999WO-JP03984	W	19990726	<--	

OS MARPAT 132:208130

GI



I

AB The title compds. I [R1 and R2 represent each hydrogen, alkyl, cycloalkyl, etc.; and Y1 and Y2 represent each hydrogen, alkylthio, cycloalkylthio, alkoxy, etc., or one of Y1 and Y2 represents hydrogen and the other represents hydroxy, alkoxy, cycloalkoxy, etc., or Y1 and Y2 together represent oxygen or X(CH2)nX (wherein X represents oxygen or sulfur; and n is 2 or 3)] are prepared These compds. are useful as drugs for treating and preventing psychiatric disorders such as schizophrenia, anxiety, depression and bipolar disturbance, and neurol. diseases such as drug addiction, cognition disorder, Alzheimer's disease, Huntington's disease, Parkinson's disease, movement disorder in association with muscular rigidity, brain ischemia, brain insufficiency, spinal cord lesion and head disorder. (1RS,2SR,5RS,6RS)-2-Amino-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid in vitro showed ED50 of 34.2 nM in suppressing the accumulation of cAMP in CHO cells expressing mGluR2 receptor.

IC ICM C07C-229/50
ICS C07D-339/06; A61K-031/195; A61K-031/38

CC 34-2 (Amino Acids, Peptides, and Proteins)
Section cross-reference(s): 1

IT Antidepressants
Antipsychotics
Anxiolytics
(aminofluorobicyclohexanedicarboxylic acid derivs. with effect on group-2 metabotropic glutamate receptor)

IT **Glutamate receptors**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(metabotropic; preparation and bioactivity of aminofluorobicyclohexanedicarboxylic acid derivs. with effect on **group-2** metabotropic glutamate receptor)

IT **Schizophrenia**
(preparation and bioactivity of aminofluorobicyclohexanedicarboxylic acid derivs.)
RE.CNT 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L60 ANSWER 13 OF 14 HCAPLUS COPYRIGHT 2007 ACS on STN
AN **1999:495267** HCAPLUS
DN 131:130284
TI Preparation of fluorine-containing amino acid derivatives as group-2 metabotropic glutamate receptor agonists
IN Nakazato, Atsuro; Kumagai, Toshihito; Sakagami, Kazunari; Tomisawa, Kazuyuki
PA Taisho Pharmaceutical Co., Ltd., Japan
SO PCT Int. Appl., 33 pp.
CODEN: PIXXD2
DT Patent
LA Japanese
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO---9938839	A1	19990805	1999WO-JP00324	19990127 <--
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	RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
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	AU----734812	B2	20010621		
	CA---2318800	A1	19990825	1999CA-2318800	19990127 <--
	CA---2318800	C	20051220		
	JP--11279129	A	19991012	1999JP-0019137	19990127 <--
	EP---1052246	A1	20001115	1999EP-0901877	19990127 <--
	EP---1052246	B1	20030402		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
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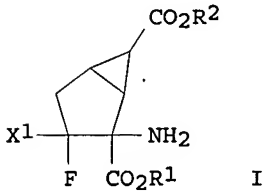
	PT---1052246	T	20030630	1999PT-0901877	19990127 <--
	ES---2191412	T3	20030901	1999ES-0901877	19990127 <--
	US---6316498	B1	20011113	2000US-0601131	20000727 <--
	HK---1036792	A1	20050603	2001HK-0107767	20011106 <--
PRAI	1998JP-0015444	A	19980128 <--		
	1999WO-JP00324	W	19990127 <--		

OS MARPAT 131:130284
GI



I

AB Fluorine-containing amino acid derivs. represented general formula (I), pharmaceutically acceptable salts thereof or hydrates of the same (wherein X1 represents hydrogen or fluorine; and R1 and R2 are the same or different and each represents hydrogen or lower C1-10 alkyl) are prepared These compds. are useful as drugs, in particular, group 2 metabotropic glutamate receptor agonists for treating and preventing psychiatric disorders such as schizophrenia, anxiety, and their associated diseases, depression, dipolar disturbance, and epilepsy, and neurol. diseases such

as drug addiction, cognition disorder, Alzheimer's disease, Huntington's chorea, Parkinson's disease, motility disturbance associating muscular stiffness, cerebral ischemia, cerebral insufficiency, spinal cord lesion, and head disorders. Thus, optical resolution of (1SR,2SR,3SR,5RS,6SR)-2-spiro-5'-hydantoin-3-fluorobicyclo[3.1.0]hexane-6-carboxylic acid by formation of the diastereomeric salt with (R)-(+)-1-phenylethylamine followed by acidification of the salt with aqueous HCl to gave (1S,2S,3S,5R,6S)-2-spiro-5'-hydantoin-3-fluorobicyclo[3.1.0]hexane-6-carboxylic acid which was heated with 60% aqueous H2SO4 at 140° for 2 days to give (1S,2S,3S,5R,6S)-2-amino-3-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid (II). II in vitro showed ED50 of 23.65 nM for suppressing the accumulation of cAMP in CHO cells expressing mGluR2 metabotropic receptor.

IC ICM C07C-229/50
ICS A61K-031/195; A61K-031/215
CC 34-2 (Amino Acids, Peptides, and Proteins)
Section cross-reference(s): 1
IT **Glutamate receptors**
RL: BPR (Biological process); BSU (Biological study, unclassified); MSC (Miscellaneous); BIOL (Biological study); PROC (Process)
(metabotropic, mGluR2; preparation of fluorine-containing amino acid derivs. as **group-2** metabotropic glutamate receptor agonists for treating and preventing psychiatric disorders and neurol. diseases)
IT Alzheimer's disease
Anticonvulsants
Antidepressants
Antipsychotics
Anxiolytics
Drug dependence
Gastrointestinal motility
Glutamate agonists
Parkinson's disease
Schizophrenia
(preparation of fluorine-containing amino acid derivs. as group-2 metabotropic glutamate receptor agonists for treating and preventing psychiatric disorders and neurol. diseases)
RE.CNT 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L60 ANSWER 14 OF 14 HCAPLUS COPYRIGHT 2007 ACS on STN
AN **1998:583442** HCAPLUS
DN 129:285933
TI Reversal of phencyclidine effects by a group II metabotropic glutamate receptor agonist in rats
AU Moghaddam, Bita; Adams, Barbara W.
CS Dep. Psychiatry, Veterans Administration Med. Center, Yale Univ. Sch. Med., West Haven, CT, 06516, USA
SO Science (Washington, D. C.) (**1998**), 281(5381), 1349-1352
CODEN: SCIEAS; ISSN: 0036-8075
PB American Association for the Advancement of Science
DT Journal
LA English
AB Glutamatergic abnormalities have been associated with several psychiatric disorders, including schizophrenia and addiction. Group II metabotropic glutamate receptors were targeted to normalize glutamatergic disruptions associated with animal model of schizophrenia, the phencyclidine model. An agonist (LY354740) of this group of receptors, at a dose that was without effects on spontaneous activity and corticolimbic dopamine neurotransmission, attenuated the disruptive effects of phencyclidine on working memory, stereotypy, locomotion, and cortical glutamate efflux. This behavioral reversal occurred in spite of sustained dopamine hyperactivity. Thus, targeting this group of receptors may present a nondopaminergic therapeutic strategy for treatment of psychiatric disorders.
CC 1-11 (Pharmacology)
IT **Glutamate receptors**

RL: BSU (Biological study, unclassified); BIOL (Biological study)
(metabotropic; reversal of phencyclidine effects by a **group II** metabotropic glutamate receptor agonist in rats)
IT **Schizophrenia**
(reversal of phencyclidine effects by a group II metabotropic glutamate receptor agonist in rats)
RE.CNT 45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

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L2 22747 (B12-C10 OR C12-C10 OR B12-E02 OR C12-E02 OR B14--J01B3 OR C14-

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L4 498603 A61K045/IPC,IC,ICM,ICS,ICA,ICI OR (P86? OR M782)/MO,M1,M2,M3,M4
E OLANZAPINE/CN
L5 11 E3-16
SEL SDCN
EDIT /SDCN /DCN
L6 324 E1-11
L7 390 OLANZAPINE
L8 1606 L3,L6-7 AND L4
L9 31 L8 AND ?MGLU?
E JOHNSON B//AU
E JOHNSON B/AU
L10 431 E3,E17
E JOHNSON BRYAN/AU
E SCHOEPP D/AU
L11 15 E4
L12 5430 (ELI OR LILLY OR ELILILLY)/CS,PA
L13 5241 ELIL/PACO
L14 1 L9 AND L10-13
L15 30 L9 NOT L14
L16 21 L15 AND (PY<=2002 OR AY<=2002 OR PRY<=2002)
L17 26 L9 AND METABOTROPIC GLUTAMATE
L18 0 L17 AND L10-13
L19 19 L17 AND (PY<=2002 OR AY<=2002 OR PRY<=2002)
L20 21 L16,L19

FILE 'HCAPLUS' ENTERED AT 16:21:16 ON 04 JUN 2007
L21 1 US20050192273/PN OR (US2004-509772 OR US2002-369771# OR WO2003-

FILE 'REGISTRY' ENTERED AT 16:22:18 ON 04 JUN 2007

FILE 'HCAPLUS' ENTERED AT 16:22:18 ON 04 JUN 2007
L22 TRA L21 1- RN : 14 TERMS

FILE 'REGISTRY' ENTERED AT 16:22:18 ON 04 JUN 2007
L23 14 SEA L22
L24 1 L23 AND OLANZAPINE
L25 106 C17H20N4S AND SC4-C6-NC2NC3/ES
L26 106 L25 AND NC2NC2/ES

FILE 'HCAPLUS' ENTERED AT 16:23:33 ON 04 JUN 2007
L27 2339 LANZAC OR LY170053 OR LY 170053 OR OLANZAPIN# OR ZYPREXA
L28 2049 L26
E ANTIPYCHOTIC/CT
E ANTIPSYCHOTIC/CT
E E6+ALL
L29 13587 E15+OLD,NT

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L35           1 WY1094 OR WY 1094
L36        1040 QUETIAPINE
L37       30003 L27-30,L33-36
L38        4304 ?MGLU?
                E GLUTAMATE RECEPTORS/CT
                E E3+ALL
L39        2549 E11+OLD (L) ?MGLU?
L40         444 E15+OLD,NT
L41         265 L37 AND L38-40
                E JOHNSON B/AU
L42         189 E3,E20-21
                E JOHNSON BRYAN/AU
L43          70 E3,E6-7
                E SCHOEPP D/AU
L44         232 E3-9
L45       15300 L12
L46          20 L41 AND L42-45
L47         245 L41 NOT L46
L48          77 L47 AND (PD<=20020403 OR PRD<=20020403 OR AD<=20020403)
                E DRUG INTERACTION/CT
                E E4+ALL
L49       58732 E5+OLD OR E10+OLD,NT
L50       33260 L49 (L) (?COMBIN? OR ?SYNERG?)
L51           3 L48 AND L49-50
                E GLUTAMATE RECEPTORS/CT
                E E3+ALL
L52         476 E11+OLD (L) GROUP (1A) (II OR III OR 2 OR 3)
L53          24 L52 AND L37
L54          10 L53 AND (PD<=20020403 OR PRD<=20020403 OR AD<=20020403)
L55           1 L54 AND L49-50
L56          10 L54-55
L57          24 L53-56
L58           3 L57 AND L42-45
L59          21 L57 NOT L58
                SEL AN 4 6 9 11-21
L60          14 L59 AND E1-28
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=> b hcap
FILE 'HCAPLUS' ENTERED AT 15:14:47 ON 05 JUN 2007
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FILE COVERS 1907 - 5 Jun 2007  VOL 146 ISS 24
FILE LAST UPDATED: 4 Jun 2007  (20070604/ED)

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 This file contains CAS Registry Numbers for easy and accurate
 substance identification.

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L19  ANSWER 1 OF 1  HCAPLUS  COPYRIGHT 2007 ACS on STN
AN   2003:818322  HCAPLUS
DN   139:302068
TI   Therapy for psychoses combining an atypical antipsychotic and an mGlu2/3
     receptor agonist
IN   Johnson, Bryan Glenn; Schoepp, Darryle Darwin
PA   Eli Lilly and Company, USA
SO   PCT Int. Appl., 42 pp.
     CODEN: PIXXD2
DT   Patent
LA   English
FAN.CNT 1
     PATENT NO.          KIND   DATE        APPLICATION NO.        DATE
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             CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
             GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,
             LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM,
             PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT,
             TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
         RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY,
             KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES,
             FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR,
             BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
     CA---2478227          A1    20031016    2003CA-2478227         20030321
     AU2003218063          A1    20031020    2003AU-0218063         20030321
     EP---1492595          A1    20050105    2003EP-0714045         20030321
         R:  AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
             IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK
     JP2005528378          T     20050922    2003JP-0581846         20030321
     US2005192273          A1    20050901    2004US-0509772         20040928
PRAI 2002US-369771P        P     20020403
     2002US-369797P        P     20020403
     2003WO-US07283        W     20030321
AB   The invention provides a pharmaceutical composition and methods for treating
     psychosis comprising the combination or a first component which is an
     atypical antipsychotic with a second component which is a mGlu2/3 receptor
     agonist.  The invention also provides a pharmaceutical composition and method
```

of treating a psychiatric disorder comprising the combination of a first component which is an atypical antipsychotic with a second component which is a compound which allosterically enhances receptor activity for mGlu2 and/or mGlu3.

IC ICM A61P-025/18
ICS A61K-045/06; A61K-031/551; A61K-031/196

CC 1-11 (Pharmacology)
Section cross-reference(s): 63

IT 5786-21-0, Clozapine **132539-06-1, Olanzapine**
176199-48-7 191471-52-0 **611168-14-0**, LY 404039 611168-15-1
611168-16-2 611168-17-3, LY 459477 611168-18-4 611168-19-5
611168-20-8 611168-21-9 611168-22-0
611168-23-1
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(atypical antipsychotic-mGlu2/3 receptor agonist combination for treatment of psychoses and psychiatric disorders)

RE.CNT 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> d his

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L1 1 US20050192273/PN

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FILE 'HCAPLUS' ENTERED AT 13:41:19 ON 05 JUN 2007
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L4 3 C10H14N2O7S AND L3
L5 42 C10H14N2O7S
L6 5 L5 AND C3-SC4/ES
L7 106 C17H20N4S AND SC4-C6-NC2NC3/ES
L8 1 L6 AND L7
L9 4 L6 NOT L8
L10 3 L9 NOT MXS/CI

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L12 2055 L7

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E OLANZAPINE/CN
L13 1 E3

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E OLANZAPINE/CT
E E3+ALL
L15 2037 E9
L16 2379 L12,L14-15
L17 1 L8
L18 1 L16 AND L11
L19 1 L17-18

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